20.	Mihael POLYMEROPOULOS	Novartis
21.	Lembit RAGO	WHO, Switzerland
22.	Jens S. SCHOU	University of Copenhagen, Denmark
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25.	Jacek SPLAWINSKI	Narodowy Instytut Zdrowia Publicznego, Poland
26.	Noboru TAKAHASHI	National Institute of Health Sciences, Japan
27.	Mieko TAMAOKI	Yamanouchi
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29.	Jan VENULET	CIOMS, Switzerland
30.	Mark WATSON	Merck & Co
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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.
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4. Dr Kerwin Low, Assistant Director Centre for Drug Administration, Health Sciences Authority, Singapore.
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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:
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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:
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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:
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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.

The code key linking the double coded pharmacogenetic samples and information is kept by a third party. This should not be the investigator in possession of the key linking coded sample and/or information to the subject.

The key to the double code might be maintained by the sponsoring organisation, in areas entrusted with maintaining confidential information (e.g. legal, quality assurance, clinical statistics) under strict operating procedures. Alternatively, the key might be held by an external entity, such as governmental agency, legal counsel, or other qualified third party not involved with the research.

The individual can only be linked with the sample or data obtained from it by bringing the two code keys together. Although the samples do not carry any information on the identity of the subject, it is still considered to be possible to identify the subject as long as both code keys exist.

As with single coded samples, the existence of a link between the pharmacogenetic data and the subject's identity makes it possible to withdraw a sample or data (up to the time the results stemming from that data are reported), update subject information, return results and inspect the process. However, the conditions under which the pharmacogenetic information might be linked back to the subject's identity for any purpose are determined strictly by the specifics of the research protocol. These conditions should be explicitly described in each protocol, and included within the subject's informed consent.

4.4 Anonymised samples and data

are for practical purposes double coded samples where the key linking the first and/or second code is deleted. They may be also previously single coded samples where the single code key is destroyed or even previously identifiable samples where the name/identifier is removed.

Anonymised samples and data do not carry any longer personal identifiers. Once the linking key has been deleted, information related to the subject's identity is no longer linked to data related to the pharmacogenetic results. This offers an additional level of security to the individual's data.

After anonymisation it is not possible to withdraw a subject's sample from analyses, to update subject information for further use, or to return any individual results to the subject or the subject's physician. Similarly, it also is not possible to inspect the study to determine that pharmacogenetic data is accurately correlated to a specific subject.

There will be times when stored samples may provide a regulatory agency additional information related to clinical outcome. The ability to link individual data to a patient will be essential in some circumstances and anonymised samples would be a problem.

In general, anonymised samples are well suited to research studies in which hypotheses are generated, but may be less so for clinical trials on which label claims are based.

4.5 Anonymous samples and data

are those that do not have any link whatsoever between the sample and the individual identity.

Anonymous samples may have population information (e.g., the samples may come from subjects with diabetes) but no individual data that might allow the identity of the subject to be traced. The clinical information is limited to broad categories of data, such as "male, age 50-55, cholesterol > 240mg/dl". In many instances, the sample has no clinical data at all.

This situation is applicable in cases where the population is large enough and measures are taken in building up the code (see recommendations on page 3 on reconstructing a link).

Anonymous samples are useful in some types of pharmacogenetic studies.

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Annex 7

Pharmacogenetics and Pharmacogenomics in Japan

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1. Guidelines

1. Notifications regarding pharmacogenomics from the Ministry of Health, Labor and Welfare (MHLW)
   1.1 Clinical Pharmacokinetic Studies of Pharmaceuticals (June 1, 2001)
   1.2 Methods of Drug Interaction Studies (June 4, 2001)

   Both of these notifications are concerned with genetic polymorphisms. The necessity to accumulate know-how on pharmacogenomic methods and to create an organization for this purpose is also described.

   On 8 June 2004, the Ministry of Health, Labour and Welfare published for consultation purposes a guidance note entitled "Submitting information of clinical trials which used pharmacogenomic approaches to the regulatory agency for making the guidance of pharmacogenomic approaches on pharmaceutical developments (Draft)". They requested that comments be submitted by 9 July 2004.

2. Guidelines on Bioethics
   There are one law and six ethical guidelines significant to the promotion of pharmacogenomics in Japan
   2.1 Personal Information Protection Law (May 23, 2003)
   2.2 Fundamental Principles of Research on The Human Genome (June 2000)
   http://www.mext.go.jp/a_menu/shinkou/seimei/index.htm
   2.3 Ethics Guidelines for Human Genome/Gene Analysis Research (April 2001) (Currently being translated – draft is now available)
   2.4 Ethical Guidelines for Performing Human Genetic Testing Contracted to the Japan Registered Clinical Laboratories Association (April 2001)
   2.5 Ethical Guidelines for Epidemiological Research (June 2002)
   2.6 Guidelines for Clinical Studies (July 2003)
   2.7 Guidelines for Genetic Testing, by The Japan Society of Human Genetics, Council Committee of Ethics (August 2003)

The Personal Information Protection Law was legislated in May 2003. It has been suggested that this law does not apply to fields of scientific research or matters concerning public health and hygiene. Therefore, at present, the necessity of a separate law or guideline is being considered.

Among the guidelines listed above, "Ethical Guidelines for Human Genome and Gene Analysis Research" enforced in April 2001 is the most important. This guideline is under review, as the Personal Information Protection Law shall take effect as of April 1, 2005. This guideline, regulating human genome/gene analysis, demands the compliance of researchers in these fields. The basic policies are as follows: 1) respect for human dignity, 2) adequate prior explanation, and consent by one's own free will (informed consent), 3) complete protection of personal information, 4) the research conducted shall be useful to society and shall contribute to human intellectual advancement, health and welfare, 5) priority shall be placed on the protection of individual human rights rather than social/scientific benefits, 6) assurance of study adequacy by preparation of and compliance with study protocols based on the guideline, after their review and approval by an independent ethical review board, 7) assurance of study transparency by third-party monitoring of study performance at each site and by publishing study results. Clinical studies and post-marketing surveillance are regulated by the Pharmaceutical Affairs Law, and are thus excluded from the guideline.

2. Projects to establish a foundation for pharmacogenomics

1. The International Hap Map Project
   1.1 Schedule: FY2002- FY2004 (3-year term)
   1.2 Participant: U.S., U.K., Japan, Canada, and China
   1.3 Aim: clinical application of 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. Japan will bear one-quarter of the responsibility for analysis. The data will be published in 2004.
   1.5 Project Leader in Japan: Nakamura, Yushuke (The University of Tokyo Institute of Medical Science)
2. Project on Realization of a Medical Care System in Accordance with Genetic Information
   2.1 Schedule: FY2003- FY 2007 (5-year term)
   2.2 Budget: 20 billion yen
   2.3 Aim: optimising drug therapy based on elucidating a patient's genetic constitution
   2.4 Scope: SNPs that are related to drug efficacy, onset of adverse reactions, and diseases will be elucidated using DNA and serum obtained from approximately 300,000 patients, covering 40 diseases, including cancer and diabetes, with the prior informed consent of each patient.

2.5 Project Leader: Nakamura, Yushuke

3. Cancer Epidemiology Research
   Full-scale cancer epidemiology research is scheduled to be initiated from 2005 with a programme for the collection of gene samples from 100,000 people nationwide.

4. Pharma SNP Consortium (PSC)
   4.1 Period: FY2000- FY 2002 (3-year term)
   4.2 Budget: 1 billion yen
   4.3 Aim: promotion of research on pharmacokinetic-related Japanese genetic polymorphisms, especially frequency analysis, in an ordinary Japanese population, the formation of a pharmaceutical research and development base, and contributions to healthcare in Japan via promotion of genome research
   4.4 Results: frequency analysis results were obtained for 4,272 SNPs in 202 pharmacokinetic-related genes. These will be published internationally in December 2003. The Human Science Research Resources Bank (HSRRB) has had 996 cell lines established and deposited so far. The methods for functional analysis of CYP and transporter mutant proteins have been standardised.
   4.5 Participants: forty-three JPMA (Japan Pharmaceutical Manufacturers Association) member companies

3. Activities

1. MHLW: Internal study meeting consisting of the MHLW and the Pharmaceuticals and Medical Devices Agency (PMDA) to consider the measures for making use of pharmacogenetics
2. Japan Health Sciences Foundation (HS): A working group investigation on genomics; several reports were issued and a symposium was held to promote pharmacogenomics.
3. Japan Medical Association: Discussion by the Committee on the Handling of Human Genetic Information on the enactment of an individual law to protect individual patient information to be used for medical research, etc.
4. JPMA
   4.1 A symposium to promote pharmacogenomics (June, 2004 in Kyoto)
   4.2 Drug Evaluation Committee: internal study meeting
   4.3 Research & Development Committee: internal study meeting

4. Present situation of pharmacogenomics by the industry in Japan

According to the HS report entitled "Toward Clinical Application of Pharmacogenomics", the present status of the clinical development of compounds using genome information in Japan is as follows. With reference to compounds currently under development or slated for development, 16 companies are investigating or are scheduled to investigate the effect of genetic polymorphism clinically. With regard to drug metabolising enzymes, 4 clinical studies are already underway, and 6 studies are expected to begin in the near future. With regard to drug reactions, 3 clinical studies are already underway, and 7 studies are expected to begin in the near future. These results suggest the possibility that clinical studies incorporating genetic polymorphism will increase rapidly in the next 1 or 2 years. Five companies plan prospective studies for their commercially available drugs. The objective is to identify responders and non-responders and to identify an association with the development of specific adverse reactions. The reason why most other members are not planning such studies is that they have, as yet, no appropriate candidates.

1. Examples of Clinical Usage
   1.1 Trastuzumab: IHC and FISH tests, used to select patients to whom trastuzumab should be administered, are covered by health insurance and have already been used in clinical practice.

2. Clinical Research
   2.1 Troglitazone: Troglitazone, a drug for the treatment of type II diabetes, was forced to be withdrawn from the market in March 2000, due to liver toxicity. Sixty-eight SNPs in 51 candidate genes gathered from the blood samples of 110 patients were analysed and the results indicated that SNPs in the metabolic enzymes GSTT1 and GSTM1 might play a role in the development of this liver toxicity.
   2.2 Imatinib mesilate: A method for predicting the therapeutic effects of imatinib mesilate by gene expression in each subject has been developed.
   2.3 Gefitinib: Clinical trials to investigate therapeutic effects based on changes in gene expression have been performed since 2001, and projects to identify SNPs related to acute lung injury have just started.
   2.4 Pioglitazone: Projects to identify SNPs related to the effectiveness and adverse reactions of pioglitazone, a member of the thiazolidinedione class of insulin-sensitizing agents, has started. The discovery should allow for tailor-made medicines as well as new drug development.

3. Clinical Trial
   3.1 Post-marketing clinical trial: omeprazole, lansoprazole (*H. pylori* eradication therapy, CYP2C19)

4. Development of Diagnostic Kits
   4.1 Interferon (hepatitis C treatment): prediction of therapeutic effect
   4.2 Irinotecan (anticancer drug): prediction of severe toxicity.

Annex 8

Pharmacogenetics and Pharmacogenomics in the Republic of Korea

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1. Guidelines

1. Bioethics and Biosafety Law (to be effective in January 2005)
   1.1 A National Bioethics and Biosafety Review Committee will be established under direct control of President by the law. The guideline will request institutional bioethics review board be established in each institution dealing with embryo, gene bank and gene therapy, etc. (article 6 and article 10)
   1.2 Facilities testing genetic information should receive quality accreditation by minister of Ministry of Health and Welfare. Genetic tests of scientific ambiguity that may mislead test subjects are prohibited. Genetic testing of embryo or foetus is allowed only for the diagnosis of heredity disease that Presidential decree decides. (Article 24 and article 25)
   1.3 Genetic information must not be used to differentiate individual in social activities such as education, employment, promotion, or insurance. The genetic test or the submission of the test result must not be forced. The director or employee of facilities performing genetic test must not release the genetic information of a person to another without proper justification or must not use the information for improper purpose. (Article 31 and article 35).
2. Research Guideline for Functional Analysis of Human Genome
   http://www.elsikorea.org/, http://www.koreabioethics.net/ (June 2002)
   The essential contents of the guideline are focused on several issues. (1) Specimens from human beings can be used in human genome research. (2) Another issue is autonomy or the right of self-determination of the potential subjects. When researchers select the human subject, they must respect his/her autonomy. To protect the potential subject's autonomy, researchers must get the informed consent. (3) The third issue is to protect the individual's genetic privacy. To protect the individual's genetic privacy, the genetic information must not be linked with the individual's medical record. And the disclosure of individual's genetic information must be banned. (4) The IRB (Institutional Review Board) can be a responsible body to control the scientific quality of research and the ethical and/or legal problems of research. (5) And researchers can use the genetic counsellor system to assist in getting informed consent, resolving the conflicts between researchers and subjects, and so on.
3. Korean Association of Institutional Review Boards (KAIRB's): comprehensive guideline for IRB Standard Operating Procedures (February 2003) was published as a monograph by KAIRB.

2. Projects to establish a foundation for Pharmacogenomic research

1. Korean Pharmacogenomics Research Network (KPRN)
   1.1 Schedule: FY2003- FY2011 (9-year term)
   1.2 Budget: 21 million USD for 9 years
   1.3 Aim: Discovery of polymorphisms related to drug safety and efficacy in Korean population and clinical application of pharmacogenomics information.
   1.4 Scope: 5 specific pharmacogenomic research centers focused on adverse drug reaction, drug metabolism, drug transporter, respiratory drug, and CNS drug pharmacogenomics.
   1.5 Project Leader: Professor Sang-Goo Shin (Seoul National University)
2. National Research Laboratory for Pharmacogenomics
   2.1 Schedule: FY2003- FY2007 (5-year term)
   2.2 Budget: 3.3 million USD for 5 years
   2.3 Aim: Application of pharmacogenomics to clinical practice.
   2.4 Scope: Relations of pharmacokinetics and pharmacogenomics.
   2.5 Project Leaders: Professor Jae-Gook Shin (Inje University) and Hyong Doo Shin (SNP Genetics Inc.)
3. Hap Map Project
   3.1 Schedule: FY2003-2008 (5-year term)
   3.2 Budget: 9 million USD for 5 years
   3.3 Participant: JE Lee (DNA Link, Inc.), JJ Hwang (Samsung), KY Song (Ulsan Univ), JM Yang (Seongkyunkwan Univ.), and CB Kim (NIH bioinformatics)
   3.4 Aim: Haplotype and LD mapping (Chromosome based + gene based approach) of Korean genome
   3.5 Scope: As a start, chromosome 22 is targeted (about one million genotyping/year, about 10,000 SNP/year)
   3.6 Project Leader: Kyuyoung Song (Ulsan University)
4. The Center for Functional Analysis of Human Genome
   4.1 Schedule: FY1999-FY2009 (10-year term)
   4.2 Budget: 90 million USD for 10 years
   4.3 Aim: Large-scale isolation of genes and proteins associated with diseases most characteristic of Korean populations. Identification of candidate target genes from in-depth functional analysis. Development of novel, genome-based diagnostics and therapeutics. Establishment of tech-

nological basis on which to build the national competitiveness in bio-industry and by which to contribute to the improvement of human welfare
4.4 Scope: genomic research on gastric and liver cancers, etc.
4.5 Project leader: Hyang-Sook Yoo (KRIBB)

5. Disease and Pathogenic Microbe Genomics
5.1 Schedule: FY2001 – FY2011 (10-year term)
5.2 Budget: 62 million USD for 10 years
5.3 Aim: Disease and pathogen related functional genomics
5.4 Scope: 11 disease specific genomics centers and 3 pathogenic microbe specific genomic centers
5.5 Project management: Ministry of Health and Welfare, National Institute of Health
5.6 Project coordinator: Professor Yangsoo Jang (Yonsei University)

3. Activities

1. Ministry of Health and Welfare; funding the Korean pharmacogenomics research network, disease genomics, pathogenic microbe genomics, proteomics research center.
2. KFDA (Korean Food and Drug Administration); preparing guideline for application of pharmacogenomics in drug regulation
3. Ministry of Science and Technology; funding National Research Laboratory for Pharmacogenomics, planning to fund the research in the toxicogenomics in non-clinical field
4. Academia
4.1 Pharmacogenomics Research Study Group was established in June 2001 with over 100 members working at universities and drug industries. Regular research seminar and symposia are arranged by the network.
4.2. PharmacoGenomics Research Center (PGRC) was established in January 2003 in Inje University, Busan.
4.3 International symposia:
4.2.1 Yonsei Biomedical Symposium: February, 2003, Seoul
4.2.2 Pharmacogenomics: Impact on clinical trial – October, 2003, Seoul
4.2.3 Pharmacogenomics: A step toward personalised pharmacotherapy – February 2004, Busan, organized by KPRN and PGRC.

4. Pharmaceutical Industry

Many drug discovery and genotyping bio-ventures are investing in this field. Several bio-ventures are applying the genotype to clinical practice. Multinational pharmaceutical companies are sponsoring several clinical trials searching any relation between drug efficacy/adverse effect and specific genotypes. A global pharmaceutical company sponsored a genotype-phenotype association study of CYP enzymes using probe drugs as cocktail administration. The study was done in Caucasian, Japanese and Korean, simultaneously. Pharmacogenetics/genomics is becoming an important issue in new drug approval especially related to the ethnic sensitivity of a drug by ICH E5 foreign clinical data acceptance guidance.

Annex 9

Pharmacogenetics and Pharmacogenomics in Singapore

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1. Relevant laws and regulations

1. No specific laws on pharmacogenetics research

2. Regulations governing clinical trials of medicinal products:
http://www.hsa.gov.sg/html/business/00000000000000001901.html
2.1 Medicines Act
2.2 Medicines (Clinical Trials) Regulations
2.3 Singapore Guideline for Good Clinical Practice

2. Guidelines on bioethics

1. No specific guidelines on pharmacogenetics.

2. Other relevant guidelines and reports:
2.1 National Medical Ethics Committee (NMEC) Ethical Guidelines for Gene Technology (2001)
http://app.moh.gov.sg/pub/pub03.asp
2.1.1 Provides guidelines for introduction of genetic testing into clinical practice, reviewing research protocols involving gene technology and on gene therapy.
2.1.2 For genetic testing, guidelines recommend 1) genetic counseling for patient and/or family; 2) informed consent; 3) determination of any objection to use test material for research purposes; 4) respect for wishes of key relative in regard to pedigree analysis; 5) determination of whether subject wishes to know test results; 6) guidelines for disclosure of genetic test results; 7) gene examined is associated with disease in question, test is validated and useful test results obtained; 8) advertising and marketing of predictive gene test strongly discouraged.

2.2 NMEC Ethical Guidelines on Research Involving Human Subjects (1997)
http://www.moh.gov.sg/nmec/NMEC94_97.pdf (Annex IV/D
Provides guidelines for ethics committees in the review of research proposals in order to ensure rights and welfare of subjects are protected. Accepted by the Ministry of Health and sent out to all hospital ethics committees.

2.3 Bioethics Advisory Committee (BAC) Report on Human Tissue Research (2002)
http://www.bioethics-singapore.org/resources/reports.html
Provides recommendations on tissue research that includes 1) adopt the ethical principles of primacy of the welfare of donor, informed consent, respect for human body, donations to be outright gifts, ethical review of research proposals and access requests and confidentiality; 2) conduct of research in approved institutions; 3) statutory regulations and authority for research tissue banking; 4) continuing professional and public dialogue.

2.4 BAC Consultation Paper on Research Involving Human Subjects (released for consultation in 2003)
Proposes a national framework for the ethical review by statutorily formalised ethics committees of all human clinical research proposals in Singapore.

3. Advisory boards

1. National Medical Ethics Committee
http://www.moh.gov.sg/nmec/nmec.html
Set up in 1994 by the Ministry of Health (MOH) to provide advice to MOH on ethical issues in medical practice.

2. Bioethics Advisory Committee
http://www.bioethics-singapore.org/
Appointed by the Singapore Cabinet in 2000 to examine and make recommendations to the Ministerial Committee for Life Sciences on potential ethical, legal and social issues arising from research in biomedical sciences in Singapore.

4. Projects & Activities

Some government initiatives include the set up of a national DNA and tissue repository, i.e. the Singapore Tissue Network, in 2002 to advance Singapore's genomics initiative through the collaboration between the Agency for Science, Technology and Research (A*STAR), the Genome Institute of Singapore (GIS) and Genomics Collaborative, Inc. This network has links to 5 national disease registries covering cardiology, oncology, myopia, stroke and nephrology. Other tissue repositories to provide researchers with samples of RNA and DNA include the National Cancer Centre (NCC) and National University Hospital/National University of Singapore (NUH/NUS) tissue repositories.

The Genome Institute of Singapore, set up with the support of A*STAR in 2000, is the national flagship programme in the genomic sciences in Singapore and is involved in looking for novel gene targets through SNP analyses and disease associations. Other institutes involved in genomic research include the Institute of Cell and Molecular Biology, Bioinformatics Institute as well as academic institutions, e.g. National University of Singapore.

Because of the ethnic diversity in Singapore, a significant portion of the pharmacogenetic research focuses on elucidating genetic differences influencing drug response and disease susceptibility among different ethnic groups, i.e. Chinese, Caucasians, Indians and Malays.

1. Singapore Tissue Network http://www.stn.org.sg/

2. National Cancer Centre tissue repository and research projects
http://www.nccs.com.sg/Rsch/DMS_tissue.htm
http://www.nccs.com.sg/rsch/rsch_therapy.htm

3. National University Hospital/ National University of Singapore (NUH/NUS) tissue repository
http://www.med.nus.edu.sg/path/tissues/welcome.htm

4. Genome Institute of Singapore
http://www.gis.a-star.edu.sg/homepage/gistechnology-intro.jsp

5. Institute of Cell and Molecular Biology
http://www.imcb.a-star.edu.sg/research/research_group/index.html

6. National University Hospital pharmacogenetic research
   6.1 Projects include pharmacogenetic research with respect to optimising anticancer drug utilization, with particular interest in differences in drug behaviour among Asian ethnic representations.
   6.2 Current approach is to have phenotype for all subjects genotyped, and to fully sequence key candidate genes, including promoter, exons and exon-intron junctions, 3'UTR.
   6.3 Recent data on CYP2C9, which is the 3rd most important drug metabolising enzyme after CYP3A and CYP2D6, has been submitted. Many novel variants were found, and the gene patterns were different between the Indians (who are similar to the Caucasians), and the Chinese and Malays.

6.4 Project collaborations with the US-based Pharmacogenetics Anticancer Agents Research (PAAR) Group, who are sponsored by the National Institute of General Medical Sciences (NIGMS), National Institutes of Health.

7. National University of Singapore
http://www.med.nus.edu.sg/phar/dept/staff/academic/Lee_EJD/homepage.htm
http://www.med.nus.edu.sg/research/progrsch/hum_mol_genetics.shtml
Some examples of research projects carried out in the Pharmacogenetics Lab, NUS include:
   7.1 target gene approach, identifying and characterising polymorphisms affecting genes regulating drug metabolism, drug transporters and ion channels involved in long QTc syndrome
   7.2 systematic characterisation of novel genetic variants in Chinese, Malays and Indians
   7.3 functional characterisation of variant transporters and ion channels through cultured cell systems and patch clamp electrophysiology
   7.4 establishing Hapmap for MDR1 and MRP1 and 2 genes through collaboration with the National Cancer Centre

5. Present situation in Singapore – Clinical Trials

1. 20 clinical trials incorporating pharmacogenetic research have been received from both pharma industry (16) as well as hospitals/institutions (4) during the period of 2003 to 1st quarter of 2004. This constitutes about 15% of all trials reviewed by HSA in the same period.

2. Of the 20 clinical trials, 10 are phase I trials, 4 are phase II trials and 6 are phase III trials. 16 of the studies are currently ongoing with 3 studies pending regulatory approval. One study has been withdrawn by sponsor.

3. The trials can be broadly categorised into the following types of studies:
   3.1 Genotyping e.g., CYP2D6, to exclude low responders (n=1)
   3.2 Genotyping of specified candidate genes, e.g. drug metabolising enzymes, transport proteins, target protein, to determine influence on drug pharmacokinetics or for interpretation of trial results (n=9)
   3.3 Exploratory analysis (candidate genes not specified) including possible whole genome scans to identify genetic biomarkers that can predict drug pharmacokinetics, clinical safety, drug response, clinical outcome, prognosis (n=10)

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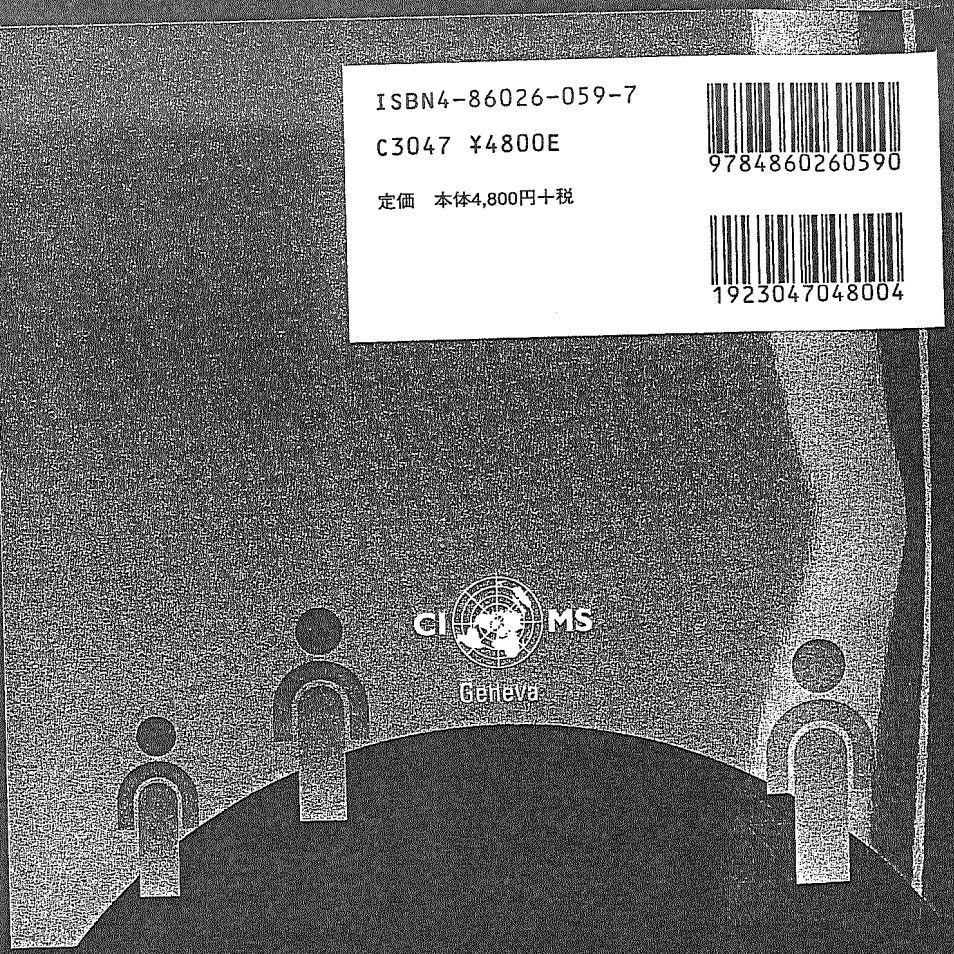

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監訳 はじめに

本書は、国際医科学協議会（Council for International Organizations of Medical Sciences: CIOMS）から2005年2月に発行された“Pharmacogenetics - Towards improving treatment with medicines”の日本語訳である。

ここでは、まず内容を簡単に紹介し、つぎに日本ではあまり知られていないCIOMSの組織、原本を作成したCIOMSのファーマコジェネティクス・ワーキンググループ（CIOMS Working Group on Pharmacogenetics: CIOMS WG on PG）について触れ、最後に翻訳プロセスについて述べる。

本書が取り上たトピックは、ファーマコジェネティクスに関連した、副作用、開発、行政、倫理、経済、教育など全部で12章と、大変幅広い。一般に、ファーマコジェネティクスはその技術的側面が注目されている。ところがその技術的な進歩が、必ずしも現在の医療体制や臨床試験の中で十分には組み込まれていない。このことに対する疑問は日本のみならず世界レベルでも存在するものであるが、本書では、ELSI（ethical, legal and social implications）とも称される、倫理的、法的、社会的側面が大変よく書かれている。

特に第8章「遺伝子検査実施、遺伝データ、遺伝情報」と第9章「倫理的課題」で述べられている「遺伝子例外主義」（genetic exceptionalism）に対する見方は注目される。「遺伝子例外主義」とは、遺伝情報は他の医学情報と比べ特別であり、そのため特別の保護を必要とする見解を示す。しばしば日本では「究極の個人情報」と称される、誤解に基づき形成された「遺伝子」に関する人々の認知が、パブリックヘルスに好ましくない影響をもたらすことを、丁寧に解説している。「情報コンテンツ」が重要なのであり、遺伝情報も他の医学情報と同じく情報保護がなされるべきであると提言している。この「反遺伝子例外主義」は今後日本でも議論されるべきトピックであり、本書がそのきっかけになろう。

また、オーストラリア、カナダ、中国、台湾、EU、日本、韓国、シンガポールの状況を紹介するAnnexが含まれる。アジア諸国のcountry reportを本書に含むことは日本から提案したもので、そこでの状況がシステマティックに紹介されるのも本書がはじめてである。

CIOMSは、1949年に世界保健機関（World Health Organization: WHO）と国連科学教育文化機関（United Nations Educational, Scientific and Cultural Organization: Unesco）が共同で設立したnon-profit（NPO）でnon-governmental（NGO）の組織である。3種類のメンバーから構成される。第1は、国際学会などのメンバー（international member）で、国際内科学会（International Society of Internal Medicine）や世界医師会（World Medical Association: WMA）などの18機関が含まれる。第2に各国の医科学を代表する機関