Working Party on Biotechnology

AN INTERNATIONAL PERSPECTIVE ON PHARMACOGENETICS: THE INTERSECTIONS BETWEEN INNOVATION, REGULATION AND HEALTH DELIVERY

Issues and Background Paper for the Workshop

17-19 October 2005

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Context

1. This issues paper was prepared for the OECD workshop entitled “An International Perspective on pharmacogenetics: The intersections between innovation, regulation and health delivery”, to be held in Rome, Italy on 17–19 October 2005.

2. The aim of this paper is to provide a short introduction to some of the key policy issues raised by current and future applications of pharmacogenetics and to stimulate debate on the topics to be considered at the workshop. This paper will form the introductory part of a more extensive policy report to be produced following the workshop. The policy report, directed to government and industry, will address the opportunities and challenges to health innovation and health delivery systems posed by developments in pharmacogenetics. The report will draw on this paper and the presentation and discussions at the Rome Workshop and will be prepared by the OECD Secretariat.

3. The objectives of this workshop are therefore to:

- Communicate the current status of pharmacogenetics research internationally.
- Analyse and raise awareness of the anticipated impacts (both opportunities and challenges) of pharmacogenetics on innovation, health delivery and health care systems.
- Review regulatory issues, challenges and opportunities that may arise in translating the outputs of pharmacogenetics research into useful products for targeted therapies and diagnostics.
- Identify initiatives and strategies relevant for pharmacogenetics development and implementation to improve the delivery of health innovation and public health across OECD countries with particular attention to medium-term developments in health innovation policy, regulation and access.
Introduction

4. Advances in human genomic research coupled with breakthroughs in fields that span biomedical as well as computational biology are resulting in a greater understanding of the natural history of disease and of the causative mechanisms involved. These advances will transform the practice of medicine, the ways in which disease is prevented, diagnosed and treated and the ways in which health care services are delivered.

5. So dynamic are these developments that in 2004 OECD Science and Technology Ministers and Health Ministers recognised that an increased understanding and use of human genomics is required if nations are to achieve the dual goals of economic growth and development of policies that deliver better health outcomes.

6. A major concern for governments is to ensure that the introduction of genomic innovations balances public health benefits as well as social and economic consequences and that they have the knowledge base to make rational policies and choices based on evidence.

7. It is in this context that the OECD Working Party on Biotechnology concluded there was a need to consider the opportunities and challenges that arise from the applications of pharmacogenetics. Information derived from pharmacogenetics is expected to improve the overall efficiency of the drug development process and should result in a better understanding of drug efficacy and adverse drug reactions (ADRs), to the benefit of patients, healthcare systems and drug developers.

8. The use of such information is the latest in a series of developments that are likely to continue that make an increasing use of evidence linking intervention and clinical outcome – thus the increasing use of evidence-based medicine.

9. These changes – and the rate and pace at which they occur – have the potential to profoundly change the shape of the market for pharmaceuticals as well as outcomes. However, if the opportunities offered by such developments are to be captured and the challenges met, then public policy and practice as well as industry policy and practice will have to go through a period of joint evolution. Whether or not such evolution is co-operative between public and private sectors as well as across borders may make a fundamental difference to the extent to which the promise of genomics to deliver better health is attained as well as to the extent to which there is a successful return on public and private investment in the Human Genome Project and other similar ventures.

10. Pharmacogenetics will be one of the first products of the Human Genome Project and Haplotype Map Project to reach clinical utility and is a key step in the process towards more evidence-based development of medicines. This is therefore an appropriate point at which to address the policy impacts of the applications of human genomic research now and in the medium term.¹

11. Research on pharmacogenetics will have implications for the productivity and competitiveness of pharmaceutical companies. The implications could be significant as there are implications on the costs of pharmaceuticals, and because of the significant economic effect of adverse drug reactions. In the short term, there is a need for a systematic evaluation of the costs and benefits associated with the introduction of pharmacogenetic testing to guide drug prescribing. There is also a need to develop policy frameworks, to accommodate the complexities of ethical views and of cultural and population diversity in different OECD member countries.

12. These, and other arguments, indicate that patients, regulators, providers, insurers, the research community, and the pharmaceutical industries all have an interest in gaining an understanding of the ways in which advances in pharmacogenetics will impact on the discovery, development and use of new medicines as well as the continuing use of products already on the market.

13. The development of such policies in the short term will have implications too for the development of evidence-based medicines and targeted therapies in the medium to long term. Such short-term decisions should not be taken in isolation. The OECD Rome workshop will attempt therefore to look both at the short-term (particularly regulatory) opportunities and challenges, but also at the medium term ones (for health symptoms, for businesses and for patients) as well as the cross-linkage between the short, medium and, to the extent possible, the long term.

What are Pharmacogenetics and Pharmacogenomics?

14. Pharmacogenomics and pharmacogenetics are rapidly evolving disciplines that are intimately linked to the advances being made in genomics-based science and technology and the field of translation and medicine. They provide a new body of knowledge and new tools for improving the efficiency of the drug discovery process, increasing the number of drugs available and improving their safety and/or efficacy, i.e. the prescribing risk/benefit ratio.

15. Although the terms pharmacogenomics and pharmacogenetics are often used interchangeably and may vary from document to document, it is worth identifying their scope and meaning for the purpose of this report and debate in order to understand the impact of each discipline.

16. Pharmacogenetics may be defined as ‘the study of the effects of genetic differences between individuals in their responses to medicines in terms of their metabolism (pharmacokinetics) or action (pharmacodynamics)’. It is likely that such genetic factors account for between 20% and 95% of the observed responses, depending on the drug and the genotype of the target population. Other factors such as age, co-morbidity and the simultaneous presence of other substances will also influence an individual response to a particular drug.

17. Pharmacogenomics aims to systematically assess through constantly emerging and evolving genomic technologies how interacting systems of genes may affect pharmacological function and therapeutic drug response. It provides a focus on the molecular responses generated by different drugs expanding the tool-kit currently available for the evaluation of preclinical safety and pharmacology testing.

18. In crude terms, pharmacogenetics is about identifying the best medicine for a specific disease occurring in a patient population with a particular genotype. Pharmacogenomics is about genetic markers that may diagnose, stage, and classify disease in the context of drug responses and attempts to optimise the identification of those drugs in the discovery pipeline that induce the most appropriate pharmacological responses. Research on pharmacogenetics could impact on both new and existing medicines. Pharmacogenomics is expected to have a major impact on the drug discovery procedures currently used by the major pharmaceutical companies.

19. This paper is predominantly concerned with pharmacogenetics and its twin objectives of improving the safety and the efficacy of new and existing medicines but in policy terms this cannot and must not be separated from the longer-term opportunities and challenges to health care delivery.
Prospects for Pharmacogenetics

20. The growing understanding of the genomic mechanisms contributing to drug responses, including non-response or toxicity, offers new opportunities for drug development and health care. Pharmacogenetics is seen by many as an area that takes up these opportunities. Research is thus progressing at a rapid pace. Much of the enthusiasm and support appears justified as expected outcomes include:

- Maximising drug response and minimising adverse effects.
- Increasing the tools available for an evidence-based rational approach to healthcare.
- Reducing the size and timing of clinical trials.

21. Many however fail to see the immediate clinical returns and health care impacts, and contend there are significant practical and technical challenges to overcome before pharmacogenetics and pharmacogenetic testing is introduced into mainstream healthcare. Getting the enabling environment right will need focused analysis of health care and regulatory systems, and careful consideration of how application and diffusion of pharmacogenetics might impact on these.

Clinical Implications

22. The economic burden of adverse drug reactions (ADRs) is significant. In the United States the cost of drug-related morbidity and mortality exceeded USD 177.4 billion in 2000. Hospital admissions accounted for nearly 70% (USD 121.5 billion) of total costs, followed by long-term-care admissions, which accounted for 18% (USD 32.8 billion).²

23. A significant number of ADRs are discovered only after the drug has reached the market. This is not altogether surprising since regulatory authorities approve drugs on the basis of population data on efficacy and safety and on a broad assumption that all patients are a homogenous group. In reality, however, there are wide variations in individual response often arising from two key elements of the dose-response relationship of the drug: pharmacokinetics and pharmacodynamics.

24. Pharmacokinetics describes the course of drug and metabolite levels in different tissues, and can be viewed as the speed at which an individual metabolises a drug. Pharmacodynamics describes where (the site/target) and how (the mechanism) a drug acts on the body.

25. For example, polymorphic variations³ in genes may affect the binding of drugs to particular cellular receptors and hence whether the drug can enter a cell or tissue or the kinetics of this process. These variations may also affect the rate at which a drug is metabolised and hence either activated, inactivated or rapidly excreted. These effects may determine to what extent an individual responds to a particular drug, and ultimately the treatment efficacy and clinical utility of the drug. Equally, polymorphic gene variations may determine whether the drug itself or any generated toxic products are retained by the body for prolonged periods to produce adverse side reactions. Pharmacogenetic studies are therefore important for improving our understanding on both drug efficacy and drug safety.

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³ A polymorphic variation is a specific DNA sequence variation; polymorphisms occur frequently throughout both coding and non-coding regions of the genome and most are benign with regard to function.
26. A clear example is provided by the cytochrome P450 isoenzyme super family, which exists in over 50 forms and is responsible for determining the susceptibility to pharmacokinetic responses in a significant number of currently licensed drugs as well as those in development. The distribution of the cytochrome P450 genetic variants differs markedly between different individuals and ethnic groups, accounting for some of the differences seen in the effectiveness of many treatments.

27. The variant genes and their enzyme products can be classified into those which produce catalytic activity that is normal, abolished, decreased, increased or somehow qualitatively altered. This can be most easily seen with cytochrome P450 2D6 (CYP2D6) which influences the metabolism of approximately 20% to 25% of all drugs in current clinical use. A lack of this enzyme results in the reduced effectiveness of the analgesics tramadol and codeine. It will also lead to the decreased clearance of some tricyclic antidepressants and may result in cardiotoxicity. Conversely, individuals with multiple gene copies of the CYP2D6 gene will rapidly metabolise these compounds and will tend not to respond to therapy when given ordinary doses due to difficulties in retaining therapeutic levels of the drug in the plasma.

28. A contrasting example where a somatic mutation as opposed to an inherited mutation is an important pharmacogenetic determinant involves the use of trastuzumab (Herceptin). Herceptin is a humanised monoclonal antibody approved for the treatment of metastatic breast cancer, that targets and blocks the function of HER2 protein over expression.

29. Research has shown that HER2 positive breast cancer is a more aggressive disease with a greater likelihood of recurrence, a poorer prognosis, and a decreased chance of survival compared with HER2 negative breast cancer.

30. Some 30% to 40% of women with breast cancer over-express the HER2 oncogene as a result of the malignant transformation. Treatment with Herceptin significantly improves the overall survival rate amongst this group and is ineffective in the 60% to 70% of women who do not over-express the drug target.

31. Efficacy of Herceptin is therefore dependent on altered HER2 gene regulation in the tumour of the patient and hence the prerequisite for choosing this therapy is a gene test that more or less predicts who is likely to respond to the drug. This is not an all or nothing parameter, which points to some of the difficulties that might be encountered when determining which patients to include or exclude from treatment. This emphasises the fact that as with many clinical variables, pharmacogenetics will provide probabilistic and not absolute information for prescribing and will have to be utilised in conjunction with other medical information. Pharmacogenetics therefore looks to increase the probability of a correct decision being made.

32. Even so, pharmacogenetics is progressing at a rapid pace. Examples of other marketed treatments requiring pharmacogenetic input include Gleevec, a drug designed to treat patients with chronic myeloid leukemia (CML) involving the 'Philadelphia chromosome' translocation; a test linking hypersensitivity reactions to the HIV/AIDS drug Abacavir to the HLA-B*5701 haplotype, BiDil an orally-administered nitric oxide-enhancing medicine that has been demonstrated to improve outcomes for African-Americans diagnosed with heart failure and the dosing of Strattera for Attention Deficit Hyperactivity Disorder.

33. It will be essential to draw lessons learned from these early products, particularly to understand the evidence base needed for uptake across different health care systems and jurisdictions, the impacts on clinical care and health outcomes and fully understanding the impact of pharmacogenetics upon the risk/benefit ratio for an adverse as opposed to improved efficacy.
Ethical Implications

34. In the past three years considerable attention has been paid to the ethical implications of research in pharmacogenetics. A number of international and national organisations and institutions have reviewed the ethics and potential socio-economic impacts of pharmacogenetics. Among them are the Nuffield Council on Bioethics, the European Society of Human Genetics Professional and Public Policy Committee, the Council for International Organisations of Medical Sciences (CIOMS) Working Group on Pharmacogenetics and Pharmacoeconomics, and the European Commission’s DG Research’s programme on Science and Society.7

35. The emphasis on ethical issues is perhaps not surprising given the current public debate on the use of genetic information. Pharmacogenetics, as further discussed in subsequent sections raises some important social and ethical questions relating, for example, to the storage of DNA samples and genetic data, the reshaping of trials based on genotypes of patient groups, informed consent with such trials, clinical inclusion and exclusion within drug delivery regimes, equity of health care delivery. It is important that dialogue on these issues is initiated in a timely way, while pharmacogenetics is still in its early days.8

36. OECD’s Working Party on Biotechnology has engaged in work relevant to these debates, specifically on the development of guidelines on the quality assurance of genetic testing, as well as the proficiency of those offering such tests, and guidelines on the management and governance of human genetic research databases.

Technological Developments

37. Scientific progress is often limited by the technologies available. Advances in DNA sequencing technologies have been a key to the determination of the complete nucleotide sequence of the human genome and the identification of polymorphisms within it.

38. Rapid single nucleotide polymorphisms (SNPs) mapping, high-throughput, multiplexed assays using microarrays, improved statistical analysis and bioinformatics all play a vital role in pharmacogenetics. Further advances in these areas will facilitate the more rapid and economic detection

6. The Group has as members eight senior scientists from drug regulatory authorities namely: the Agence du Médicament, France; EMEA, London; the Federal Institute for Drugs and Medical Devices, Germany; the Food and Drug Administration (FDA), USA; Health Canada, Ottawa; the Institut Lekow, Poland; the Medicines Control Agency (MCA), London; and the National Agency for Medicines, Finland; three senior scientists from academia: Dr. Margarete Fisher-Bosch-Institute, Germany; University of Tokyo, Japan; and the University of Copenhagen, Denmark; ten senior scientists from the pharmaceutical industry (Abbott Laboratories, USA; Bayer AG, Germany; F. Hoffmann-La Roche Ltd., Switzerland; Gencell-Genomics, France; GlaxoSmithKline, UK; Merck & Co. Inc., USA; Pfizer, USA; Schering-Plough, USA; Serono International SA, Switzerland; and Yamanouchi Pharmaceutical Company, Japan); and representatives of WHO and the CIOMS Secretariat.
8. The OECD report Health Technologies and Decision Making points to the need to develop a receptive policy framework for new technologies well before they are presented into the market if market access and uptake is not to be delayed.
of genomic polymorphisms that are associated with cellular and whole-organism responses following the administration of drugs.

39. A microarray is a tool for analyzing DNA or RNA. Generally microarrays consist of a small membrane or piece of glass containing anything from several hundreds to hundreds of thousands of specific DNA sequences that have a functional significance in the context of the human genome. In expression assays the microarray exploits the ability of a given mRNA molecule, also known as a transcript, to bind specifically to, or hybridize to complementary DNA probes on the microarray. By using an array containing many different probes, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of active genes within a cell by measuring the amount of transcript mRNA bound to each site on the array. With the aid of bioinformatics and computer programmes, the amount of mRNA bound to the probes on the microarray can be measured precisely generating a profile of gene expression in the cell.

40. Currently much of microarray data is produced in various formats and units and is normalised and analysed in different ways. Consensus on terminology, data transfer and presentation methods for DNA sequence information was driven by the human genome project which accelerated the development of shared and public databases. In the area of microarray expression analysis no single unifying international project has accelerated consensus building until recently, when the External RNA Controls Consortium (ERCC) and the Microarray Gene Expression Data (MGED) were formed. These groups include major microarray users and developers and are focused on building consensus and driving forward the establishment of common terminology, and standard formats about a microarray experiment. A major aim of these efforts is to promote the sharing of high quality, comparable genomic data within the life sciences and medical research communities. Priority technical issues to be resolved are the development of reference control materials, international standards for gene annotations, and bioinformatics software.

41. Development of efficient and rapid SNP screening tests in a user-friendly standardised form are also needed if arrays are to be accepted as tools for clinical trials and patient care.

42. In addition, large population-based data sets of linked molecular and clinical information will have to be established for a variety of scientific and public purposes to help turn hypothesis into valid data that can verify the correlation between genomic variations and drug-related effects. Generation of the databases containing pharmacogenetic information and clinical databases will therefore need to occur in parallel alongside statistical considerations for signal detection (as previously noted, the OECD is currently working on guidelines for the management and governance of such databases).

43. This in turn will draw attention to the interoperability of these different databases and the ways in which pharmacogenetic information will be collected and used by researchers and regulators and what information will be subsequently needed by health professionals. A key question for patients is whether it will be possible to prevent pharmacogenetic profiling from providing unauthorised access to sensitive disease-related genetic information.

**Implications For Drug Development**

44. For the past decade there has been increasing concern about the productivity of the pharmaceutical R&D process. Other debate around the use of pharmacogenetics focuses on the safety and efficacy of new and existing drugs. A number of initiatives are under way that aim to address this issue. OECD member country Science and Technology and Health ministers see the creation of a better match between public and private sector investments in health innovation, health policy and health outcomes as a set of key policy objectives. The OECD workshop on Health Innovation held in Berlin in November 2004,
referred to the “re-invention of the clinical research and innovation enterprise” and saw pharmacogenetics as a significant driver in achieving this.

45. Pharmacogenetic data will be relevant to most stages of the drug development process. It will facilitate the identification of molecular biomarkers that can predict drug response, differentiate and rank compounds for development and reduced attrition, accelerate preclinical and clinical studies and identify those individuals best able to benefit from therapy and/or dosing schedules. Hence pharmacogenetics provides opportunities for informed decision making along the whole pharmaceutical pipeline including post-approval development and monitoring.

46. It is also likely that pharmacogenetics will lead to a re-evaluation of the clinical trial methodologies used to obtain the data necessary to gain regulatory approval, including the correlation with other biomarkers and clinical outcomes and a greater understanding of the assessment of medicinal risk/benefit. This holds out the potential for much more targeted, efficient and effective trials held over shorter periods.

47. Prospective genotyping of volunteers is becoming an important component of Phase I drug development at many pharmaceutical companies. By doing so, sponsors, for example, can learn early on if there are potential tolerance and safety issues with individuals in the general population who are poor metabolizers as there are lack of efficacy issues in rapid metabolisers.

48. During phase II and III trials, genotyping is used with other inclusion/exclusion criteria to help identify those individuals who will/will not benefit or tolerate therapy due to inherited differences in either metabolism or the pharmacological target (e.g. receptor), to define various dose regimes and to compare with non-stratified trial designs.

49. One of the outcomes of identifying a pharmacogenetic response to a drug during its development may be the need to co-develop a suitable diagnostic test that may or may not be marketed alongside the drug after it has been licensed. Some of the issues involved have already been considered in a preliminary concept paper published in 2005 by the Food and Drug Administration in the United States. This paper reviews the likely changes in the type and amount of data needed to obtain regulatory approval of new drugs, particularly when these are associated with the co-development of pharmacogenetic tests.

50. A number of methodological questions associated with clinical trial protocols remain to be defined. These include the parameters of recruitment into clinical trials. Their size, duration and endpoint will need to be explored on a case by case basis for specific indications. As the frequency of some genetic polymorphisms relevant to drug metabolism varies in different ethnic populations, the generalisability of the data generated in clinical trials necessitates regulatory consideration before introduction into a new population. The ability to conduct pharmacogenetic analysis will assist in this aim yet may add complexity to the studies required when drugs are submitted for licensing in a new jurisdiction. Uncertainty about requirements may actually impact adversely on trade and reduce the number of new drugs reaching the global market place. This number is already declining because of drug discovery problems experienced by the pharmaceutical industry in general.

51. Furthermore, the potential for pharmacogenetics and genomics to encourage disease or patient stratification may in certain cases restrict the market size for a drug thus changing the dynamic from one of ‘block-buster’ drug to a more diversified portfolio impacting the structure and dynamics of the industry. On the other hand, in the long term, this may be balanced by reducing attrition and increasing probability of development success in the industry and increased revenue owing to more product approvals or by identification of new pathways or useful targets for the development of new classes of medicines active on several diseases sharing that pathway and thus improved clinical outcomes.
52. Understanding of pharmacogenetics may also allow pharmaceutical companies to pursue drugs previously discarded during the development phase or withdrawn because of toxicity to specific patient sub-groups or uncertainties around efficacy that can be defined by their genotype.

53. The changing dynamics of market structure (even without further market intervention by purchasers) and the increasing ability to co-market complementary products (diagnostics and therapeutics, for example) certainly will pose opportunities and some challenges to the pharmaceutical industry. How regulators react to such developments, in terms of pricing, intellectual property rights, licensing and market access – amongst other factors – will in turn have implications not just for the structure and functioning of health systems, but for the extent to which technological developments can deliver better health care as well as for the investment and marketing decisions taken by industry.

**Impact On Healthcare Systems**

54. The translation and integration of pharmacogenetics into routine clinical care is essential if the potential benefits are to be gained.

55. This will require an appreciation of the associated opportunities and challenges. Pharmacogenetics is essentially predictive, and therefore is a component of the shift from reactive to predictive healthcare that is often cited as the potential major benefit of the genetic revolution. Furthermore, pharmacogenetic data can be used to identify an appropriate dose for different subsets of patients and individual patients, and thus generally improve the risk/benefit ratio of drug therapies.

56. Challenges arising from pharmacogenetics, on the other hand, include concerns about liability and the necessity for physicians to learn how to prescribe drugs based on molecular profiles. There is a risk that funders and insurers will limit reimbursement to “optimal populations”.

57. Although it is likely that pharmacogenetics is likely only to affect specific therapeutic areas and drugs in the short term, it is reasonable to assume that the technology will eventually be applied to both common and chronic diseases. This will necessarily create both technical and educational challenges for health professionals and will require change in the ways in which healthcare is delivered.

**Rate of adoption and potential determinants**

58. The rate at which pharmacogenetics is adopted will depend not only on the evidence base available to support the technology but also on stakeholder perspectives and national variations in the health care systems in different OECD member countries.

59. Decision makers in health care are increasingly concerned with the effect of health care technologies on outcomes for patients and with the value for money of those technologies. Thus, a factor that will influence the development of pharmacogenetics will be the extent of recognition by both decision makers and the medical community of the need for safer and more effective drugs; and the potential of pharmacogenetics to determine on a rational basis which interventions work and which do not. In addition, pharmacogenetics will be relevant to both existing medicines and drugs under development. It is uncertain how the balance between the use of pharmacogenetics to reduce adverse events and its use for drug

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discovery will be achieved and, in the case of existing medicines, who should take responsibility for supporting the necessary research and development.

60. Another factor that will determine the rate of diffusion of pharmacogenetics will be coverage policies, in particular the sorts of reimbursement policies and cost-containment strategies that are pursued in drug and test use policies and clinical guidelines. Payers will have to determine whether to require genetic testing before initiating certain drug therapies and may require that formularies consider the relative trade-offs. The clinical utility and economic benefits of introducing pharmacogenetics into mainstream health care are, however, currently uncertain. The application of pharmacogenetic testing to the prescription of new drugs may make them more expensive. On the other hand, the consequential costs of inappropriate prescribing or the results of adverse reactions may more than offset the added costs of the pharmacogenetic tests resulting in increased clinical value to the patient and prescriber. Studies on the health economics of pharmacogenetics and on the cost benefit ratio of pharmacogenetic testing will be needed to provide an appropriate evidence base.

Infrastructure Needs and Training Programmes

61. Successful integration of pharmacogenetics will also depend on appropriate infrastructure and trained personnel. Pharmacogenetics research data is, by its very nature, information intensive. Prior to clinical application, methodologies and systems must be implemented to meet the demand for accessible, accurate and timely information that can be collected, aggregated and exchanged for analysis and decision support in the clinic. This will be aligned with the current need for interoperating electronic medical record systems. Basic informatics and computer science tools that can help with this transformation of medical record keeping have already been developed. However, much informatics research needs to be done to develop and deploy an infrastructure that will scale and integrate pharmacogenetics smoothly into practice. In addition it is clear that standards for encoding and processing information must be the cornerstone of facilitating pharmacogenetics research and related applications. These goals will also require better integration of genomics and biomedical informatics into curricula for physicians and clinical providers in general. Moreover, the delivery of pharmacogenetic testing may initially necessitate greater involvement in patient care by healthcare professionals other than the general practitioner. Healthcare professionals may need to be identified who are able to interpret how pharmacogenetic tests results relate to the available prescription medicines and then advise as appropriate both the prescribers and the patient. This means that greater emphasis will need to be placed on genetics and pharmacogenetics in undergraduate and postgraduate medical, nurse and pharmacist training.

62. The discipline of informatics-based genetic care and “genomic medicine” will have to become key parts of a physician’s training. The need for public education in this field has never been greater.

Patients’ Perspectives

63. Finally, patients are the ultimate consumers of health care technology and although many are aware of or interested in genetics testing, will they actually agree to pharmacogenetics and more targeted therapies? How will they get the information needed to understand the concept? One indication that demand for genetic technologies is strong is the steady growth of genetic testing as reported by a recent OECD survey. Another indication is the increase in direct-to-consumer advertising and purchase of genetic tests. However this does not necessarily imply demand for and acceptability of pharmacogenetic


testing. Simultaneously, in some countries patients are concerned about the possibility that personal genetic information will be used in a discriminatory way by employers or to deny insurance cover or that social stigmatisation could result.

64. However, because some of the uses and benefits of pharmacogenetics remain in the exploratory phase, few attempts have been made to engage with the general public to describe the technology and indicate how it might affect both individuals and the wider patient population. This indicates that specific communication and education programmes may be needed to ensure that the use of pharmacogenetics for the development and prescription of safer, more effective medicines is fully understood.

65. This need will be significantly increased if the concept of targeted medicine is widely promulgated and if commercial laboratories begin offering pharmacogenetics tests directly to the consumer. Any such communication and education programmes will need to be carefully targeted to take account of differences in language and a range of other ethnic, cultural and societal sensitivities. The media as a whole will have a key role in providing responsible pharmacogenetic-based healthcare information to the general public.

66. Ultimately, there are significant gains to be made by engaging public debate. If patients come to consider pharmacogenetic tests relevant to key treatment decisions in the same way as they perceive routine biochemical tests, it is likely that pharmacogenetics could soon significantly affect clinical practice.

Pharmacogenetic Databases: Social and Public Policy Issues

67. One hallmark of pharmacogenetic research studies is the large amount of genetic data that must be accumulated and integrated for high-resolution drug-response genotyping and subsequent phenotype profiling. Indeed, a significant challenge for the future of pharmacogenetics will be documenting enough of the drug response variability to make genotyping clinically predictive.\textsuperscript{12} In some cases this might require information on a few polymorphisms or genes, in others it might require very complex studies that involve relatively large number of genes or a genomic-based approach. Effective sharing of exploratory data, particularly on unpublished drug studies and negative data, and multidisciplinary international networks will be needed to make research more efficient. Furthermore, if pharmacogenetics is to be useful as an approach to surveillance of adverse response to treatment, genome banks of samples for retrospective analysis and databases linking polymorphisms with suspected ADRs and other relevant clinical information will also be necessary.\textsuperscript{13}

68. In all cases protection of the rights of persons who are genotyped will have to be in place if health care providers and patients are to agree to genomic characterisation of individuals as an integral part of medicine.

69. An area where pharmacogenetic research has advanced significantly is the study of population differences in drug responses.

70. Population frequencies of many polymorphic genes of pharmacogenetic interest depend on race or ethnic specificity. Information about ethnic specificity has become an integral part of pharmacogenetic

\textsuperscript{12} Pharmacogenetics: potential for individualized drug therapy through genetics -Trends in Genetics, Vol. 19, No. 11, p. 660-666.

Many genetic factors have recently been identified that account for the effects of ethnicity on pharmacokinetics, pharmacodynamics, and drug safety.

Racial and ethnic research, particularly in developing countries, raises specific ethical and social concerns. A significant question is whether individuals in developing countries will themselves desire health benefits as a result of such study. A major determinant may be access to testing and to the medical interventions that may be identified as a result of this research. If genotyping itself becomes essential for effective deployment of therapies directed to diseases in developing countries, then it should also be provided as part of the health services directed to deal with those conditions.

Regulatory Frameworks

Access to pharmacogenetic tests will be controlled in a number of ways. The way pharmacogenetics is delivered in existing healthcare systems, the costs of the tests and their clinical utility have already been referred to. However, more formal regulatory frameworks, operating within existing legal statutory systems or through the voluntary adoption of best practice guidelines, represent another way of controlling access, and indeed introducing pharmacogenetic tests.

The statutory frameworks for the regulation or licensing of drugs, medical devices and diagnostic tests have generally evolved independently across the OECD member countries. The use of pharmacogenetics in drug development and the introduction of pharmacogenetic testing will draw attention to the need to clarify regulatory requirements worldwide and identify areas where harmonisation can be achieved. Furthermore, the close association of genetic testing with pharmacogenomics will mean that regulatory bodies dealing with one should have expertise in the other.

Currently, however, whilst many pharmacogenetic initiatives are being conducted worldwide, debate on the topic is not progressing at the same rate in the various OECD countries, with the exception of the United States Food and Drug Administration (FDA), European Agency for the Evaluation of Medicinal Products (EMEA), and Japan Koseisho, which have been particularly proactive. The approach taken by these regulatory agencies provides an interesting framework for both the generation and discussion of exploratory research data.

Since 2004 the FDA has gained significant experience with a new process of consultation with industry called the Voluntary Genomic Data Submission (VGDS). Through this process, the FDA invites submission of exploratory pharmacogenomic data on drugs, or candidate drugs, to gain a better understanding of what companies are doing with genomics in drug development, and to identify questions and issues that have a significant amount of uncertainty. The FDA is committed to this process of consultation as part of a broader mandate to identify the unknown issues and questions that might represent barriers to the uptake of genomics in the drug development process. In 2005 the Agency released a preliminary concept paper on the regulatory processes, analytical and clinical issues, for co-developed drug/device combinations.

The FDA had also undertaken to organise, and to help others organise, conferences and workshops related to pharmacogenomics. As part of this effort, the FDA has recently held three public workshops co-sponsored by the Drug Information Association.

77. In Europe the EMEA released a position paper on terminology in 2002, and a leaflet written in layman’s terms. Furthermore, and similarly to the FDA, the EMEA had also begun informal briefing meetings with industry according to guidelines released in 2004 and issued for further consultation in 2005. These meetings enable early discussion to share experience and help sponsors for future regulatory submissions. Following the bilateral confidentiality arrangements between EC/EMEA and the FDA, since the 2nd quarter 2005 joint briefing meetings/VGDS discussions are being organised. Finally the agency released in 2005 a concept paper on the Development of a Guideline on Biobanks Issues Relevant to Pharmacogenetics.

78. The European Commission also considered pharmacogenetics in the report “Ethical, Legal and Social Aspects of Genetic Testing: Research Development and Clinical Applications”, calling for a conducive regulatory framework. 15

79. The Japanese Koseisho issued two guidance documents in 2001:


80. In addition, Japan Koseisho published in June 2004 a “Draft Guidance on Information Submissions for Pharmacogenetic Clinical Trial Guideline”. In this draft guidance, sponsors are invited to voluntarily submit information on the purpose of trials, target population, testing methods, and the number of subjects.

81. Finally, the Council for International Organizations of Medical Sciences (CIOMS) focused on international working group consisting of representatives from Japan, Europe and US (academicians, regulatory scientists and industry scientists). In 2005 the working group produced a multi-chapter book16 that covers a wide rage of topics – from regulatory perspectives to pharmacogenetics in drug development, and on ethics and pharmacogenetics databases worldwide.

CONCLUSION

82. Pharmacogenetics offers new ways of understanding how drugs work and how this affects both their safety and efficacy in individuals.

83. The potential opportunities from such understanding are considerable, particularly in driving a more efficient and effective clinical research and innovation enterprise. Opportunities exist to shorten clinical trials and save costs both in development terms and perhaps in terms of costs per patient treated. To capitalise on these opportunities, industry will need to be ahead of the curve on how markets are likely to change and be ready to position themselves accordingly. Some evidence of such a repositioning may already be apparent, however, and the change is more likely to be evolutionary than revolutionary.

84. Health delivery systems stand to benefit too if the potential opportunities are taken. Cost savings in terms of patient concordance, outcomes and reduced adverse drug reactions are attainable. Demand side policies will need to develop which capture these benefits in a way that is sustainable to technology providers as well as purchasers.

85. But perhaps the greatest opportunities are on offer to patients themselves, who stand to gain in terms of better diagnosis and therapy with fewer adverse reactions and more satisfactory outcomes.

86. A number of practical and technical challenges need to be overcome however before pharmacogenetics and pharmacogenetic testing become widespread in mainstream healthcare. Nevertheless, progress is being made and the idea of targeting drugs to particular sub-sets of the population is appealing (and is already happening in a small number of cases), not least because conceptually it should decrease the incidence of adverse reactions and improve health care outcomes and thereby reduce the consequential health care costs.

87. As well as opportunities, pharmacogenetics will pose a number of challenges for the industries that develop both drugs and associated pharmacogenetic tests. The clinical utility as well as commercial benefits remain somewhat uncertain and methodology for their assessment needs to be carefully developed. It will pose associated challenges for the regulatory authorities who are currently showing considerable interest in the discipline and exploring ways in which appropriate regulatory frameworks can be introduced without stifling vital innovation. Both parties will also be faced with opportunities to utilise pharmacogenetics at key decision points and need to ensure that short-term decisions do not result in long-term regrets.

88. There are also a range of social and public policy issues that may need to be resolved if potential barriers to the utilisation of pharmacogenetics and pharmacogenetic tests are to be overcome. As in all areas of health innovation, in taking decisions about pharmacogenetics care will be required to balance short- and long-term interests of the various actors mentioned throughout this report. The OECD can play a pivotal role in identifying/facilitating the international debates required to achieve such a balance so as to facilitate the increasing extent of global drug development and delivery in this area. The object of this paper, the policy report and the meeting in Rome is to stimulate these debates in this rapidly evolving discipline.
QUESTIONS AND TOPICS TO BE ADDRESSED AT THE WORKSHOP

Impact on Healthcare Systems

The translation and integration of pharmacogenetics into routine clinical care is essential if the potential benefits are to be gained.

This will require an appreciation of the associated opportunities and challenges. By better understanding patient response to medications, pharmacogenetics represents a shift from reactive to predictive healthcare that is often cited as the major benefit of the genetic revolution. Furthermore, pharmacogenetic data can be used to identify an appropriate dose for different subsets of patients and thus generally improve the risk/benefit ratio of the drug therapies.

Challenges arising from pharmacogenetics, on the other hand, include concerns of utilising information for prescribing decisions, the necessity for physicians to adjust to prescribing drugs based on molecular profiles and the degree to which insurers may limit reimbursement to “optimal populations”.

Policy Questions to be Addressed by Speakers

Impacts on Health Care Delivery Systems:

• What will be the timescale of introduction? Is pharmacogenetics an evolutionary or revolutionary process?
• Are healthcare systems ready to deliver pharmacogenetics and are they capable of responding to the associated technological advances?
• How can the benefits of pharmacogenetics be captured such that its adoption does not disrupt existing health care delivery systems across OECD member states?
• What will be the impact of pharmacogenetics on clinical care in different healthcare systems and how will pharmacogenetic testing be delivered across all clinical specialties?
• How will health care systems respond to patients seeking pharmacogenetic information outside of the profession e.g. direct to consumer/Internet sales?

Evidence-Base for Validation

• What evidence base will be needed to support the introduction of pharmacogenetics and will this affect the evidence needed to demonstrate the safety, efficacy, cost-effectiveness of both new and existing medicines? How does this relate to current systems of evaluation?
• Who is responsible for carrying out economic analyses of pharmacogenetics – the pharmaceutical industry or the health service provider? How does this relate to current systems of evaluation?
• Who will pay for pharmacogenetic tests?
• Are the methodologies for undertaking health economic analyses sufficiently well developed?
• Should economic analyses differentiate between pharmacogenetic tests that aim to identify the correct dose or those that identify a risk of adverse reactions – should the emphasis be on safety or efficacy?

**Cost-effectiveness**

• What will be the economic benefits of pharmacogenetics and will this affect reimbursement or co-funding opportunities?
• What will be the impact on health-related quality of life?
• How will cost-effectiveness/value/predictiveness be balanced?
• What will be the impact on individual health versus community public health?

**Human Resources**

For some therapies, the delivery of pharmacogenetic testing may initially necessitate greater involvement in patient care by healthcare professionals other than the general practitioner. Indeed, new healthcare professionals may need to be identified who are able to interpret pharmacogenetic tests and relate the results to the available prescribable medicines and then inform the patient. This means that greater emphasis will need to be placed on genetics and pharmacogenetics in the undergraduate and postgraduate medical, nurse and pharmacist training.

• What healthcare professionals will be involved in the delivery of pharmacogenetic services?
• Are suitable education and training programmes available and how might these change?
• Are the systems available to provide a suitable cadre of trained human resources sustainable and is appropriate manpower planning being done?

**Patients’ Perspectives**

Patients are the ultimate consumers of health care technology and although many are aware of or interested in genetics testing, will they actually understand the differences in and range of tests proposed and agree to pharmacogenetics and targeted therapies? One indication that demand for genetic technologies is strong is the steady growth of genetic testing as reported by a recent OECD survey. Another indication is the increase in direct-to-consumer advertising and purchase of genetic testing.

Ultimately, if patients come to consider pharmacogenetic tests relevant to key treatment decisions in the same way as they perceive routine biochemical tests, it is likely that pharmacogenetics could soon significantly affect clinical practice.

• Will pharmacogenetics lead to the introduction of more targeted medicine?

• Will pharmacogenetics then result in some patients being denied particular medicines? How will this be dealt with? How does this compare to current prescribing restrictions?

• What will pharmacogenetics offer the patient?

• Will the stratification of individuals through pharmacogenetic testing result in discrimination?

• How will those denied medicines on the basis of pharmacogenetics be counselled and accept the decision? How are such decisions handled currently?

**Technological Developments**

Scientific progress is often limited by the technologies available.

Rapid SNP mapping, high-throughput, multiplexed assays such as microarrays, improved statistical analysis and bioinformatics all play a vital role in pharmacogenetics. Further advances in these areas are essential to facilitate the more rapid and economic detection of genomic polymorphisms that are associated with cellular and whole-organism responses following the administration of drugs.

• What are the needs for international data interchange standards and how can these be standardised?

• How will the development of new drugs and pharmacogenetic testing platforms proceed in parallel?

• What incentives exist for disclosure of information and for data sharing?

• What are the respective roles and responsibilities of public and private sector organisations in supporting the establishment of common terminology and standard formats for pharmacogenetic research?

**Regulatory Frameworks**

The statutory frameworks for the regulation or licensure drugs, medical devices and diagnostic tests have generally evolved separately across the OECD Member states. The use of pharmacogenetics in drug development and the introduction of pharmacogenetic testing will draw attention to the need for clarifying and harmonising regulatory requirements worldwide.

• Do/Will existing regulatory mechanisms be able to accommodate pharmacogenetics?

• What is the role of the regulatory agencies in influencing the pace at which pharmacogenetics moves forward?

• What is the likelihood and impact of regulatory requirements differing in respect of pharmacogenetics? Are trans-national policies needed?

• How will the balance between innovation, regulation and sustainability be achieved?

• What will be the impact on existing approved medicines, both in volume terms and for regulators?

• Will the methodologies for clinical trials need to be revised?

• What incentives would increase the exploration and take up of pharmacogenetic innovation?
• Are there any issues associated with the ownership or licensing of intellectual property?
• How can research on existing drugs be stimulated?
• How will pharmacogenetics impact on the regulatory approvals given to existing and generic medicines?
• How will the regulators interact with prescribers to encourage informed prescribing surrounding the differences in mandated vs optional pharmacogenetic testing?

**Pharmacogenetic Databases: Social and Public Policy Issues**

One hallmark of pharmacogenetic studies is the large amount of genetic data that must be accumulated and integrated for high-resolution drug-response genotyping and subsequent phenotype profiling. Indeed, a significant challenge for the future of pharmacogenetics will be documenting enough of the drug response variability to make genotyping clinically predictive. Genome banks of samples for retrospective and prospective analysis and databases linking polymorphisms with suspected ADRs and other relevant clinical information will be necessary.

• How will pharmacogenetic data be collected, stored and retrieved?
• What information should be given to patients before they undergo a pharmacogenetic test?
• How will data sensitive to close family members be dealt with? How does this relate to comparable information generated in a health care setting?
• What ethical and culture issues are raised by pharmacogenetics and are these unique to this discipline?
REFERENCES


FDA Concept paper.


