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Pharmacogenetics and Pharmacogenomics: State-of-the-art and Potential Socio-economic Impact in the EU

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Institute for Prospective Technological Studies

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Pharmacogenetics and Pharmacogenomics: State-of-the-art and Potential Socio-economic Impact in the EU

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Acronyms

ACBI:	Association of Clinical Biochemists of Ireland
ACCE:	Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications
ADME:	Absorption, Distribution, Metabolisation and Excretion
ADR:	Adverse Drug Reaction
A&E:	Accident and Emergency
AETSA:	Agencia de Evaluación de Tecnologias Sanitarias de Andalucía (Health Technology Assessment Agency of Andalusia)
AGGR:	Advisory Group on Genetics Research
ALL:	Acute Lymphoblastic Leukaemia
AMLS:	Academy of Medical Laboratory Science
ASCP:	American Society for Clinical Pathology
BfArM`:	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMA :	British Medical Association
BNF:	British National Formulary
BUPA:	British United Provident Association
CAP:	College of American Pathologists
CBER:	Center for Biologics Evaluation and Research, FDA
CBG:	College ter Beoordeling van Geneesmiddelen (Netherlands Medicines Evaluation Board)
CDC:	Centers for Disease Control and Prevention
CDER:	Center for Drug Evaluation and Research, FDA
CDRH:	Center for Devices and Radiological Health, FDA
CB:	Cost – Benefit
CE:	European Community (refers to CE mark)
CF:	Cystic Fibrosis
CFR:	Code of Federal Regulations
CHMP:	Committee for Medicinal Products for Human Use
CISH:	Chromogenic In Situ Hybridisation
CCKL:	Netherlands Foundation for the Improvement of the Quality of Laboratory Research and for Accreditation of Laboratory Research in Medical Practice
CLIA:	Clinical Laboratory Improvements Act
CLIAC:	Clinical Laboratory Improvement Advisory Committee

CLSI: Clinical Laboratory Standards Institute

CME: Continued Medical Education

CML: Chronic Myeloid Leukaemia

CMS: Centers for Medicare and Medicaid Services

CPA: Clinical Pathology Accreditation

CPMP: Committee for Proprietary Medicinal Products

CPT: Current Procedural Terminology

CSM: UK Committee on Safety of Medicines

CT: Clinical Trial(s)

CTD: Common Technical Document

CVZ: College Voor Zorgverzekeringen (Netherlands Board for Care Insurers)

DBC: Dutch Diagnosis Treatment Combination

DH: UK Department of Health

DKV: Deutsche Krankenversicherung (German private health insurance company)

DME: Drug Metabolising Enzyme

DMMC: Dublin Molecular Medicine Centre (Ireland)

DPS: Drugs Payment Scheme

EC4: European Communities Confederation of Clinical Chemistry

EFQM: European Foundation for Quality Management

EGAPP: Evaluation of Genomic Applications in Practice and Prevention

EGFR: Epidermal Growth Factor Receptor

EMEA: European Agency for the Evaluation of Medicinal Products

EMGQN: European Molecular Genetics Quality Network

ESHG: European Society of Human Genetics

ESTO: European Science and Technology Observatory Network

EU: European Union

FAQ: Frequently Asked Questions

FDA: US Food and Drug Administration

FD&C: US Food, Drug and Cosmetic Act

FISH: Fluorescence In Situ Hybridisation

Fh-ISI: Fraunhofer Institute for Systems and Innovation Research

FMWP: Federation of Biomedical Scientific Societies

GAIC: US Genetics and Insurance Committee

GBA: Gemeinsamer Bundesausschuss (Joint Federal Commission)

GCP: Good Clinical Practice

GIST: Gastrointestinal Stromal Tumours

GMP: Good Manufacturing Practice

GLP: Good Laboratory Practice

GP: General Practitioner

GR: Health Council of the Netherlands

GVK: Gesetzliche Krankenversicherung (Statutory Health Insurance)

GVS: Dutch Medicines Reimbursement System

HIQA: Health Information and Quality Authority

HSE: Health Services Executive (Ireland)

IC: Informed Consent

ICT: Information and Communications Technology

ICH: International Conference on Harmonisation of Technical Requirements

IEQAS: Irish External Quality Assessment Scheme

IFCC: International Federation of Clinical Chemistry and Laboratory Medicine

IHC: Immunohistochemistry

IIF: Irish Insurance Federation

IMB: Irish Medicines Board

IMP: Investigational Medicinal Products

IND: Investigational New Drug

IPR: Intellectual Property Rights

IPRG: Interdisciplinary Pharmacogenomic Review Group

IPTS: Institute for Prospective Technological Studies

ISO: International Standards Organisation

ISP: International Society for Pharmacogenomics

IT : Information Technology

IVD : In Vitro Diagnostic

JCAHO: Joint Commission on Accreditation of Healthcare Organizations

LAREB: Dutch Pharmacovigilance Foundation

MA: Marketing Authorisation

MAA: Marketing Authorisation Application

MC: UK Medicines Commission

MDUFMA: US Medical Device User Fee and Modernization Act

MHRA: UK Medicines and Healthcare products Regulatory Agency

MRFG:	Mutual Recognition Facilitation Group
NDA:	New Drug Application
NEQAS:	National External Quality Assurance Scheme (Ireland)
NHIS:	National Health Information Strategy
NHS:	UK National Health Service
NICE:	UK National Institute for Clinical Excellence
NIH:	US National Institutes of Health
NSAI:	National Standards Authority of Ireland
NSF:	National Service Frameworks (UK)
NVKC:	Nederlandse Vereniging voor Klinische Cytologie (Dutch Society of Clinical Cytology)
NVVP:	Nederlandse Vereniging Voor Pathologie (Dutch Society of Pathologists)
OCM:	Organisation of Cytodiagnostics Workers
OCP:	Office of Combination Products, FDA
OIVD:	Office for In Vitro Diagnostics, FDA
PCR:	Polymerase Chain Reaction
PCT:	Primary Care Trusts (UK)
PEI:	Paul Ehrlich Institut, Germany
PGx:	Pharmacogenetics and pharmacogenomics:
PhRMA:	Pharmaceutical Research and Manufacturers of America
PMC:	Personalized Medicine Coalition
PPM:	Provider Performed Microscopy
PRTLI:	Programme for Research in Third Level Institutions (Ireland)
PT:	Proficiency Testing
PV:	Pharmacovigilance
QA:	Quality Assurance
QSR:	Quality Systems Regulation
RGO:	Raad voor Gezondheidsonderzoek (Dutch Council for Health Research)
RKI:	Robert Koch Institut, Germany
RSC:	Risk Structure Compensation
RVZ:	Raad voor de Volksgezondheid en Zorg (Dutch Council for Public Health and Healthcare)
SAGGT:	Secretary's Advisory Group on Genetic Testing (US)
SHA:	Strategic Health Authorities (UK)
SHI:	Statutory Health Insurance

SKKP:	Stichting Kwaliteitsborging Klinische Pathologie (Dutch Foundation for Quality Assessment of Clinical Pathology)
SNP:	Single Nucleotide Polymorphism
SOP:	Standard Operating Procedures
SPC:	Summary of Product Characteristics
SPRU:	Science Policy Research Unit
STT:	Stichting Toekomstbeeld der Techniek (Dutch Foundation for Futures of Technologies)
TNO:	Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek (Netherlands Organisation for Applied Scientific Research)
TPMT:	Thiopurine s-methyltransferase
UKAS:	UK Accreditation Service
UKGTN:	UK Genetic Testing Network
VGDS:	Voluntary Genomic Data Submission
VHI:	Voluntary Health Insurance (Ireland)
Vhn:	Netherlands Working Group on Immunohistocytochemistry
VSOP:	Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (Dutch Genetic Alliance)
WGP:	Wet GeneesmiddelenPrijzen (Dutch Medicines Pricing Act)

Executive Summary

The study of inter-individual specific genetic variation related to drug response (both safety and efficacy) is called pharmacogenetics. The study of genomics and proteomics information for identifying new drug targets and their mechanisms of action is called pharmacogenomics. Together pharmacogenetics and pharmacogenomics will be referred to as PGx. It is often said that advances in these disciplines could have a positive impact on the pharmaceutical and healthcare sectors by facilitating drug development and a system of personalised (individualised) medical care where drugs would be safer and more effective. However, most of the expectations surrounding the clinical application of pharmacogenetics remain unfulfilled. Only a limited number of applications have actually reached clinical practice. The potential impact on healthcare and the socio-economic implications are still uncertain. To reduce some of these uncertainties, IPTS embarked on a prospective study of this field focusing on three areas:

- Research and development status: Mapping key players, trends and outputs of academic and industrial research and development in the field of pharmacogenetics and pharmacogenomics;
- Clinical impact, in social and economic terms, of pharmacogenetics and pharmacogenomics in four EU Member States (Germany, Ireland, the Netherlands and the UK), using two case studies (HER2 and TPMT);
- Comparative review of the regulatory and quality assurance frameworks in the USA, the EU and four EU Member States (Germany, Ireland, the Netherlands and the UK).

IPTS, together with the European Society of Human Genetics, organised a workshop in March 2004 with 50 international experts from different disciplines to review the field and discuss potential socio-economic issues arising from developments in this area.[1] The workshop served to focus the abovementioned prospective study that was carried out by the European Science and Technology Observatory (ESTO). A number of tasks in the study were assigned to Michael Hopkins (SPRU, UK), Christien Enzing (TNO, Netherlands), Jim Ryan (CIRCA group, Ireland) and Sibylle Gaissner (Fh-ISI, Germany). The study group had advisory support from Detlef Niesse (Novartis, Switzerland) throughout the study.

The main findings are summarised below:

1. Research and development arena – global picture

- PGx is an important and growing field of interest in the scientific community both in Europe and in the USA. Well-known centres of excellence can be found on both sides of the Atlantic.
- The private sector is dominated by US industrial leadership, mainly by virtue of the number and size of small and medium-sized enterprises which have been developing since the early 1990s, though industrial activities in Europe have been increasing since 1998. A global search found that approximately 60% of the PGx industry is based in the USA, with most of the remaining 40% in Europe (as a percentage of the number of companies with PGx-related activities, not of their financial market share).

1 Polymorphic sequence variants in medicine: Technical, social, legal and ethical issues. Pharmacogenetics as an example. ESHG/IPTS Background document. The Professional and Public Policy Committee (PPPC) (June 2004) http://www.eshg.org/ESHG-IPTSPGX.pdf.

The EU is well-placed in PGx research, though lagging slightly behind the USA in industrial activity.

- Many companies see PGx as a useful tool in the drug development process and not necessarily accompanied by a PGx diagnostic test as an end-point. Only diagnostic companies (around one third of the total number of companies involved in PGx) see a pure market for PGx products.
- The actual utility of PGx in drug discovery remains to be seen. A patent analysis showed that only 50% of the large biotechnology firms investing in PGx in Europe and the USA held any PGx-related patent.
- Although much uncertainty remains about the impact of PGx, especially as the evidence base has yet to be developed in many areas, experts point to reduction of adverse effects as the most notable impact to be expected.
- Most experts estimated that it would take 20 to 25 years for PGx to have a significant impact on public health. They predicted that within 3 to 5 years PGx tests could be standard practice for some clinical indications, initially in oncology, where PGx has a great deal to offer in terms of improving the safety and efficacy of chemotherapeutic drugs.

PGx science is still immature. At present much research is in progress but few products with regulatory approval are on the market.

- Commercial interests are focusing primarily on the process of drug discovery and development, with little commercial interest in drug rescue (safety or efficacy), market extension strategies, post-marketing surveillance or the use of efficacy data in marketing current drugs. Academic research into PGx, on the other hand, is focused more on improving the safety and efficacy of drugs currently on the market. The main reason for this discrepancy is the lack of incentives for industry to improve drug safety and efficacy beyond the terms of their patent protection whereas academics acknowledge this topic as a primary healthcare concern.
- Companies' PGx activities are mainly science-driven rather than market-driven. Some of the companies surveyed were founded by scientists who saw a technical opportunity in this field. However, most pharmaceutical companies gradually built up PGx in-house as a specialised area of activity.

Most PGx research in the private sector is going into drug development while one of the focuses of academic research is on PGx as an end-point selection tool in treatment with current drugs.

- A high proportion of public research is financed by core funding from national governments. Industrial contracts and funds from foundations play a minor role and contribute only to individual projects. EU funding was used by under 10% of the research groups questioned. The opportunities for industry to benefit from FP6 were criticised due to the heavy administrative burden and unclear requirements and the lack of a clearly earmarked funding programme for PGx, unlike the situation in the USA.

Is EU funding being fully exploited? Less than 10% of the most active groups in PGx in Europe received finance from FP6.

- Academic research in the EU could benefit from greater unification of efforts and funding of more infrastructure. It could also benefit from improved management systems – harmonisation of ethical clearances and access to biobank collections – and systemic programme investments (PGx must be sustained over the long term as PGx research is unlikely to yield applicable results in the short term). Nearly 40% of the respondents complained about the lack of specific research programmes on PGx in Europe.
- In general, the private sector values collaboration with the public sector.

However, interviews with the industry showed that, for strategic and confidentiality reasons, only a small proportion of tasks can be subcontracted to the public sector. Experts from academia see the different research interests as one of the main obstacles to extension of industrial collaboration. Another is the scale of research. Due to financial considerations, academic circles are only able to tackle genome and PGx issues on a small scale, whereas industrial drug development processes require large integrated projects, typically involving thousands of patients, which can cover the genomic complexity.

- As a result, few public research groups collaborate with industry. Collaboration between industry and academia might need to be better promoted by appropriate European funding programmes. At the 2004 ESHG-IPTS PGx workshop a joint call was made for Commission research programmes to tackle this problem; it was agreed that it is not a matter of more funding but of more coordinated funding.

Collaboration between industry and academia on PGx knowledge and technology might need to be better promoted by an appropriate European funding programme and coordination efforts.

- In the USA and Japan the establishment of consortia forms another pillar for networking and knowledge transfer. The Japan Pharmacogenomics Consortium (started in 2003) and the NIH Pharmacogenetics Research Network (set up in 2000) provided drivers for technology transfer in PGx. The EU could benefit from similar consortia.
- A comparison between research budgets in Europe and the USA revealed that US research groups have on average twice the financial resources available to European groups. Several respondents attributed this difference to the massive activities started by the abovementioned NIH Pharmacogenetics Research Network.

- **Barriers to PGx research identified by interviews with industry**
- Low availability of DNA samples from well-characterised patients.
- Lack of clear evidence to relate drug response (both safety and efficacy) to genetic status.
- Low availability of public funding earmarked for PGx research.
- The complexities of dealing with intellectual property rights (IPR) issues on the scale involved in PGx are perceived as a major "nuisance". The process of identifying and negotiating rights to patents on DNA with a diverse group of owners is seen as burdensome by the experts interviewed.
- The high cost of PGx work. This includes the scarcity of well-trained human resources (e.g. in the field of bioinformatics), the high level of complexity (DNA sampling, data management, etc.) and the high costs of clinical studies and genotyping.
- The diversity and continuous change in the practices regarding personal data protection requirements followed by national authorities of different MS are perceived as major barriers to PGx research in the EU.
- Researchers report a mounting bureaucratic burden facing clinical trials undertaken in the EU, as well as increasing difficulty in meeting ethical and regulatory requirements. The proliferation and continual updating of protective measures, policies and guidelines at national level create further challenges for firms operating in the EU. Balancing privacy concerns with future uses of the DNA samples and adequacy of informed consent seems difficult for clinical researchers to achieve, yet is necessary to ensure the availability of data on different patient populations for drug efficacy and safety studies. Some experts call for coordination of standards of the ethical committees that oversee these processes.

2. Clinical implementation of PGx tests

Broad application of PGx in the clinic is yet to be achieved. The factors influencing clinical uptake identified in the study are:

- **Market size and the role of industry**: In the UK and Germany industry, i.e. Roche, played a very active role in introduction of the HER2 test. In the smaller markets of the Netherlands and Ireland, Roche was less active and the drive was generated by patients and doctors. Being less commercially attractive, TPMT testing had limited support from industry in the four countries analysed.

The role of industry in ensuring that diagnostic tests reach clinical implementation is essential. At the same time, the pharmaceutical industry's interest in PGx seems limited to large markets: it has pushed HER2 and Herceptin in Germany and the UK, but has been more passive on the Dutch and Irish markets. It has expressed little interest in PGx for TPMT.

- **Level of use:** Level of use varies highly between countries with different clinical protocols and acceptance levels. In Germany, Ireland and the Netherlands HER2 testing is an integral part of the breast cancer diagnosis protocol. In the UK only 35% of cancer centres routinely test for HER2 status. TPMT testing in children with ALL is not obligatory and, as a result, the frequency of testing differs between the four countries.

Level of use of testing also depends on the accepted clinical protocol, which is not the same across countries.

- **Reimbursement**: Clinical practices are subject to financial constraints. Consequently, the availability of reimbursement for PGx tests can be a crucial driver for the implementation of diagnostic technologies. In the Netherlands local hospitals have to make case-by-case decisions depending on the available budget and the uncertainty of reimbursement is perceived as a definite barrier. On the contrary, in Ireland most PGx tests are reimbursed without issue due to the small scale of activities at present.

Unclear or difficult reimbursement procedures for the tests are another major barrier to clinical uptake.

- **Patient support groups:** Patient support groups are crucial for the integration of PGx tests, as exemplified by the active role played by patients' organisations in the introduction of Herceptin. Patients are usually informed that a number of tests will be run on their tumour tissue, but HER2 testing is not specifically addressed. However, patients are increasingly informing themselves through the internet and patients' organisations and ask their doctor about Herceptin and HER2 testing.

Patient groups can influence clinical uptake by increasing awareness amongst their members who then request the treatment/test thereby increasing use.

- **Education:** Lack of education and training appears to be a strong barrier to implementation. There is little formal training or guidance for doctors and other medical staff on how to interpret PGx test results and only informal mechanisms to ensure that they understand the interpretation sufficiently.

One very big barrier to implementation is the lack of formal training and education. Introduction of a PGx test requires education of a wide range of medical staff; they have to learn to use and interpret the tests correctly.

- **Societal issues**: There is a common perception that PGx tests are less problematic in social and ethical terms than genetic tests for inherited disease. Up until now, no problems have been perceived by physicians in asking for informed consent for an HER2 or TPMT test. Nonetheless, the possibility of specific novel ethical concerns emerging in the future about particular PGx tests cannot be excluded. In particular, some future PGx tests may have consequences for first-degree

family members, raising issues of privacy and perhaps similar concerns to other forms of genetic testing for inherited disease.

- **Liability issues:** In addition, parents of children with cancer are said not to be concerned with genetic testing. However, as patients' knowledge increases, physicians might be sued for not testing children with ALL in the event of severe toxicity from 6-MP.

As more knowledge is gained about the relations between drug metabolising enzyme genotypes and the risks of adverse drug reactions, fear of liability is likely to lead to a dramatic increase in uptake of pharmacogenetics tests as a technology that helps to protect doctors against litigation.

- **Cost-effectiveness analysis:** This could be very important in levelling some of the barriers to clinical implementation. However, the economic implications of PGx have rarely been studied. In a recent systematic review of cost-effectiveness analyses of pharmacogenomic interventions in medical literature, Phillips & Van Bebber [1] identified only 11 studies that met the inclusion criteria for a cost-effectiveness analysis.
- For both HER2 and TPMT testing, an exploratory cost-effectiveness review was performed for the pharmacogenomic treatment strategy with current medical practice. For the four participating countries (Germany, Ireland, the United Kingdom and the Netherlands), information on model parameters was collected from literature and experts. The models established that both HER2 and TPMT testing are cost-effective. However, for both tests, there is no correlation between cost-effectiveness and levels of clinical implementation.
- **Clinical validity and utility:** There was wide agreement across the four case study countries that the clinical evidence base for applying PGx is underdeveloped. To confirm the clinical validity of genotype-phenotype associations, detailed research is required. However, as noted earlier, there is currently insufficient public funding for such research and lack of interest on the part of industry in developing PGx applications for drugs with expired patents.

3. Regulation of PGx products

Interviews were also conducted for comparative analyses of the regulatory and quality assurance frameworks in the USA, the EU and four EU Member States (Germany, Ireland, the Netherlands and the UK). In each country at least five, and in some cases more than ten, interviews were conducted with regulatory authorities.

- The development of PGx expertise at the EMEA and FDA appears to have been spurred by industrial enquiries. This has led to pressure to develop new capabilities at regulatory agencies issuing licences for the US, EU and other markets.
- In the USA, the FDA has been very pro-active on PGx, enlisting expert staff and issuing guidelines for PGx-related drug licensing in March 2005.
- In Europe the national agencies of Ireland, the Netherlands, the UK and Germany have received little demand directly from sponsors in relation to PGx. PGx products are being channelled through the EMEA. The EMEA draws on national agencies for its own expertise. Consequently, the lack of capability-building at national agencies could signal a need to bolster the EMEA's pool of expertise as the importance of PGx grows. So far the EMEA has been able to draw on academics and drug regulators for its PGx-related activities.
- The EMEA began focusing on PGx in 2000, using workshops with stakeholders to address emerging needs. In 2002 an expert group on PGx was established, the first to be set up by any agency. This expert group on PGx includes academic and regulatory experts

to advise on the approval of PGx-related therapeutics. The EMEA will expand its expertise to allow comprehensive assessment of PGx diagnostics in the development of drugs. However, the EMEA's licensing remit is not expected to be expanded to the approval of PGx diagnostics as "stand-alone" products.

- **Use of PGx data in licensing decisions:** It is clear from the evidence gathered in this study that almost all clinical trials carried out by large pharma now involve gathering genetic data, although this is not required for regulatory submission purposes. The FDA responded to the challenge of use of PGx data in clinical trials with its voluntary genomic data submission programme and a series of draft guidance documents, culminating in March 2005 with final release of the pharmacogenetic guidance.[2] An FDA concept paper was also recently produced on drug-diagnostic co-development.[3] Since these two sets of FDA documents were only recently released, it is too early to analyse their impact, although the study suggests that the FDA approach has been broadly welcomed by industry. However, challenges remain, notably on the validation of biomarkers, with the FDA favouring a more conservative view of what constitutes a probable as opposed to an exploratory biomarker.
- European companies hope that the EMEA will follow the FDA by issuing PGx guidelines, as clarity from the regulatory agency on what is needed is crucial for advancing PGx. In 2002 the EMEA began to discuss the use of genetic data with sponsors through one-to-one briefing meetings held outside the regulatory process. The EMEA hopes to provide further support for sponsors in the future, but there are no definite plans as yet about compulsory submission of PGx data by the EMEA.
- **Harmonisation**: Evidence from this study suggests that there appears to be general support for greater harmonisation in industry. However, industry is undecided about the time scale over which this might be achieved. Some respondents from industry were sceptical about whether harmonisation on global or even EU scale could be achieved; others were keen that it should be achieved and disappointed with progress to date, while others felt that harmonisation should not be aimed for too quickly in a field that is changing rapidly to avoid making future regulatory changes more difficult.
- **Licensing of PGx products: drug-test combination or separate approval?** The licensing of therapeutics in combination with diagnostics has presented significant challenges to the FDA. A new Office for Combination Products was established by the FDA in 2002 to address some of the emerging issues by taking the lead in combination product (drug-test or drug-device) applications. It is too early to say whether these measures have substantially addressed consistency, transparency and internal communication in the process – issues that had caused some concern. It is unclear as yet whether PGx-based drug-test products will be defined as "combination products" under US law.
- Ireland, the UK and the Netherlands already follow a single-agency approach with drugs and devices licensed by the same agency while Germany still has separate institutions. According to the EMEA, Germany's position seems to be the more common among other EU Member States, as comparatively few countries have taken the single-agency approach. In the EU the EMEA does not approve diagnostic and therapeutic combinations as the Agency does not have primary responsibility for diagnostics and its remit is limited to approval of therapeutics.

2 http://www.fda.gov/cber/gdlns/pharmdtasub.pdf accessed on 1.6.2005.
3 http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed on 1.6.2005.

- The In-Vitro Diagnostics (IVD) Directive sets out a common regulatory process for diagnostic devices in the EU which include the test component of a PGx drug-test combination. However, the EMEA is concerned that the CE mark is granted solely on the basis of technical accuracy and not of clinical utility. This is important as the evidence supporting clinical utility is regarded as one of the main challenges facing PGx.
- At present the EMEA can recommend the use of a diagnostic test as part of the labelling process. However, it is not clear how diagnostic use could be enforced in Member States or how non-marketed tests, such as "home brews" developed in hospital laboratories and outside the scope of the IVD Directive could be regulated.
- **Labelling of new medicines with PGx information and re-labelling of old products to include new PGx information.** To date there are few examples in the EU of new products requiring labelling to accommodate PGx data. When such information about PGx testing is required, there is no standardised way of presenting it on the drug's label or data sheet.
- Where new clinical data emerge which suggest that a PGx diagnostic would significantly improve the safety of a drug already available on the market, there is a legal mechanism (Article 31) that allows the EMEA to recommend a change of labelling to Member States. However, this has not yet been applied for PGx. Similarly, the FDA also has powers to revise drug labelling as new data emerge and has already issued new advice on the basis of PGx data. The FDA presently handles the need to include PGx data on the drug label on a case-by-case basis.

  In any situation where new data on a licensed drug emerge, regulators have emphasised the need to address scientific uncertainties carefully and their duty to act only on robust data.
- **Regulation of PGx testing in the clinic:** Should the clinical applications of PGx grow substantially in future years, support for quality control systems will increase and become more important. This pattern has been seen in a number of laboratory disciplines in recent years, including testing for genetic diseases.
- **Accreditation of clinical laboratories:** Accreditation schemes aim to provide an independent inspection system that reviews laboratory staff performance, infrastructure and processes to maintain service quality. Laboratory accreditation schemes have been established in the USA, Germany, the Netherlands, the UK and Ireland. The accreditation system is often voluntary or, where accreditation is encouraged, is not enforced.
- **External quality assurance (QA) schemes:** Such schemes identify laboratories that are performing poorly and provide them with assistance. QA schemes are not sufficiently developed in the USA and the EU in the area of genetic testing.[4] Unsurprisingly there are few dedicated PGx schemes as yet, although HER2 schemes are well established in the EU and USA, and a global TPMT testing scheme is being piloted by a UK laboratory. International schemes are of particular benefit to small countries which sometimes lack the "critical mass" to launch a national scheme. Support for international QA schemes could therefore be an important priority for the EU in the field of PGx.

4 IPTS (2003) "Towards quality assurance and harmonisation of genetic testing services in the EU", IPTS, Seville; OECD (2005) "Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Survey of 18 OECD Member Countries", Paris: OECD.

1. Introduction

The study of inter-individual specific genetic variation related to drug response is called pharmacogenetics. The study of genomics and proteomics information for identifying new drug targets and their mechanisms of action is called pharmacogenomics. Together pharmacogenetics and pharmacogenomics are known as PGx. It is often said that advances in these disciplines could have a positive impact on drug discovery and development allowing customisation, selection, dosing, and routing of administration of existing and new therapeutic agents thereby facilitating truly personalised medical care. Pharmacogenetics/genomics might enable the pharmaceutical industry significantly to enhance the productivity of drug discovery and development. It might also allow pharmaceutical companies to look again at drugs that have failed because of low response rates in the general population, targeting the drug at the people who respond best. In healthcare, pharmacogenetics/genomics could help reduce the overall cost of disease management for the individual and bring two main potential clinical advantages: minimised adverse effects and improved therapeutic efficacy. However, most of the expectations surrounding the clinical application of pharmacogenetics remain unfulfilled. Only a limited number of applications have actually reached clinical practice. The potential impact on healthcare and the socio-economic implications are still uncertain. To reduce some of these uncertainties, IPTS embarked on a prospective study.

As PGx is a relatively young field, a comprehensive picture of the state of the art in the EU in terms of research activities, commercial applications in drug development, structure of the pharmacogenetics-related market/industry and probable future developments has yet to emerge. An assessment of the current situation and an analysis of trends in the area of pharmacogenetics/genomics were therefore deemed necessary. IPTS, together with the European Society of Human Genetics, organised a workshop in March 2004 with 50 international experts from different disciplines to review the field and discuss potential socio-economic issues arising from developments in this area.[5] The workshop served to focus the abovementioned prospective study that was carried out by the European Science and Technology Observatory (ESTO). A number of tasks in the study were assigned to Michael Hopkins (SPRU, UK), Christien Enzing (TNO, Netherlands), Jim Ryan (CIRCA, Ireland) and Sibille Gaisner (ISI, Germany).

The ESTO study was structured around three main tasks and this synthesis report follows the same outline:

Part 1: Mapping key players, trends and outputs of academic and industrial research and development in the field of pharmacogenetics and pharmacogenomics;

Part 2: Clinical impact, in social and economic terms, of two early examples of pharmacogenetics and pharmacogenomics in four EU Member States (Germany, Ireland, the Netherlands and the UK);

Part 3: Regulatory and quality assurance frameworks: a comparative study of the USA, the EU and four EU Member States (Germany, Ireland, the Netherlands and the UK).

This synthesis report is based mainly, although not solely, on the final reports on the contributions from each partner. Their full reports and additional information can be found on the JRC-IPTS website (www.jrc.es).

5 "Polymorphic sequence variants in medicine: Technical, social, legal and ethical issues. Pharmacogenetics as an example." ESHG/IPTS Background document. The Professional and Public Policy Committee (PPPC) (June 2004) http://www.eshg.org/ESHG-IPTSPGX.pdf.

IPTS is grateful for the help and input received from Ignacio Garcia-Ribas, Detlef Niese, Marisa Papaluca and Sandy Thomas, and would like to thank especially the experts who took the time to respond to our survey or participate in interviewes.

Whilst this report represents the results of original research, parts of the analysis have drawn from prior and continuing work funded in the UK by the Wellcome Trust (grants GR061491MA, GR063308,) the Economic and Social Research Council and the Medical Research Council (grants RES-151-25-0049, PTA-037-27-0029)[6].

1.1 Methodology

1.1.1 Definitions and scope

The history of pharmacogenetics dates back to the 1950s [2]. The term pharmacogenetics is generally associated with inheritance. For example, Weilshboum and Wong [3] define pharmacogenetics as "the study of the role of inheritance in inter-individual variation in drug response". Pharmacogenomics is a term that emerged in the late 1990s and is often associated with industrial application of genomics in drug discovery [4].[7] While many have struggled to reach agreement on the precise meaning of the terms pharmacogenetics and pharmacogenomics ([4-7], FDA 2002[8]), in this report the term PGx is used to refer collectively to the science and technologies associated with dividing patients or populations into groups on the basis of their therapeutic requirements using a genetic test. It therefore includes activities related to classical pharmacogenetics as well as studies of gene expression or methods of disease stratification related to predicting drug response. Although more recently PGx has become associated with molecular genetics, in this report the definition of genetic test is not limited to methods that rely on direct DNA analysis but also includes phenotypic tests (e.g. those operating at protein, metabolite or other biomarker level, such as IHC tests and other non-genetics-based test methods) which can be used to reveal an underlying genetic change relevant during the therapeutic decision-making process. It also includes both heritable and somatic change as relevant to the field of PGx.

Pharmacogenetics and pharmacogenomics are emerging interdisciplinary areas comprising different specialities, such as medicine, IT, cell and molecular biology, genomics, epidemiology and pharmacology. According to the EMEA position paper EMEA/CPMP/3070/01 (EMEA, CPMP 2002),[9] pharmacogenetics and pharmacogenomics combine the study of inter-individual variations in DNA sequences related to drug response and the study of the variability of expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level.

Consequently, the potential applications of PGx are:

1) Research: Discovery of new drug targets and, as a result, better drugs and better determination of disease mechanisms;

2) Development: Creating tools for improving the safety and efficacy of new and existing drugs through new genomic knowledge and technologies;

3) Clinical application: Improving safety and efficacy in the clinical setting by individualising pharmacotherapy based on genomic tests.

A search term list was applied to search manually for players in the public and private sectors. The search terms were drawn from the literature review and discussions by the project

6 Further details on this body of research are available from http://www.nottingham.ac.uk/ igbis/pgx, http://www.york.ac.uk/res/pgx and http://www.sussex.ac.uk/spru/profile12105.html

7 http://www.wellcome.ac.uk/assets/wtd003274.pdf.

8 http://www.fda.gov/cder/genomics/presentations/Meeting_Workbook_10May02.pdf.

9 EMEA; CPMP (2002): Position Paper on Terminology in Pharmacogenetics. http://www.emea.eu.int/pdfs/human/press/pp/307001en.pdf, released on 21 November 2002.

team. The fields of science and technology and relevant regulatory infrastructure are rapidly changing. For the purposes of this study, the definitions of the key terms are therefore deliberately broader than those often used by practitioners and the field of PGx was delineated by the following keywords:

DNA variation, DNA sequence alteration, mutation, single nucleotide polymorphism (SNP), drug response, drug metabolism, converting enzyme, enzymatic activity, drug transport(er), human P-glycoprotein, drug receptor, disease development, drug action, drug efficacy, sensitivity, toxicity, reaction, gene expression, RNA, ribonucleic acid, drug design, drug discovery, clinical trial, disease mechanism, disease predisposition, disease pathway, pathogenesis, diagnostic tool, asthma, endothelial cell, cardiovascular disease, lipoprotein, cancer, blood-brain barrier, neurological disease, neurodegenerative disease, schizophrenia, depression, bipolar disorders, alcoholism, tobacco addiction, opioid system.

1.1.2 Research organisations

In order to identify research groups and their research topics, a three-step strategy was applied. In the first step internet search engines were used to identify country-specific internet pages. The second step continued at URL-specific and country-specific level in order to search in scientific journals, in the membership lists of national and international associations, publication databases and recent conference documentation. The third step involved matching the internet hits with the authors of scientific literature using a database of journal articles and PGx books compiled at Fraunhofer ISI.

1.1.3 Companies

The analysis of the industrial development of PGx builds on work undertaken as part of a project, funded by the Wellcome Trust, on the clinical and commercial development of pharmacogenetics [8]. This involved a survey of the global industry working in this area and identified the main ways in which firms are developing PGx technology. The ESTO survey on the global industry working in this area built on this.

All possible firms claiming an interest in PGx ("the wider PGx universe") were identified from the following sources:

- The abovementioned Wellcome Trust project (approximately 100 firms analysed in detail);
- A recently completed study of global genomics companies (over 600 firms analysed in detail);[10]
- The UK, European and North American Biotechnology Handbooks;[11]
- PGx-related alliances on the ReCap.com database;[12]
- Genetic Engineering News database of the global biotechnology industry;[13]
- Contents pages of industrial market research reports.[14]

In addition, NewsAnalyzer[15] – a database of over 150 000 press releases on the biotechnology industry - was searched for the terms pharmacogenetic*, pharmacogenomic*, personalized and personalised medicine. This generated a list of over 300 firms, which were also added to the wider search universe. Altogether, well over 1 000 firms were examined.

10 Unpublished data.
11 UK Biotechnology Handbook (2003) London: BioCommerce Data Ltd; European Biotechnology Handbook (2003) London: BioCommerce Data Ltd; North American Biotechnology Handbook (2003) London: BioCommerce Data Ltd.
12 www.recap.com.
13 http://www.gendatabaseonline.com.
14 These were found at www.marketresearch.com.
15 www.newsanalyzer.com.

It should be noted that this search protocol has proven highly effective in other studies, but it depends critically on how firms present themselves in their public documents (press releases, websites, annual reports, etc.). A very small number of firms with a minor interest in PGx could be omitted if they do not identify themselves as working on pharmacogenetics, personalised medicine or other related search terms.

1.1.4 Online survey

To gain insight into the frame conditions for PGx research, such as financing, networking and collaboration between academia and industry, the research teams identified were asked to participate in an online survey carried out in November and December 2004. The response rate averaged 27%. Low response rates (below 10%) were observed for the USA and Japan. No response was received from Norway and Austria. The poor response rate from Japanese and US research teams could be due to the low interest in European research policy as it plays no role for overseas players. The same behaviour was also experienced in telephone interviews.

Altogether 60 answer sheets could be analysed. A total analysis was carried out only for cases with too low a national response rate or where no national differences could be observed.

1.1.5 Interviews

The information compiled from desk research and the online survey was verified and completed by questionnaire-guided telephone interviews with management staff from leading companies and researchers from the high-ranking research organisations identified. The companies interviewed were chosen to represent different types of business models, research interests and geographical locations (Table 1-1).

Within each of these organisations, a senior executive responsible for pharmacogenetic activities was interviewed by telephone. Each person interviewed was provided in advance with an outline of the study and of the purpose of the interview. They held posts such as Head/Director of Pharmacogenetic or Pharmogenomic Activities (5), VP for R&D (2), CEO (2), Director of Discovery and Director of Regulatory Strategy.

An industrial perspective was sought to provide international comparisons between the regulatory environments in the EU, the USA, Japan and EU Member States through interviews with 15 firms (see Table 1.1, grey background). The firms interviewed were asked, in particular, to comment on how US policies, as set out in the FDA's 2005 guidance, and EU policies, such as the IVD Directive and frameworks developed by the EMEA, affect industry's development of PGx products.

Interviews were also conducted for comparative analyses of the regulatory and quality assurance frameworks in the USA, the EU and four EU Member States (Germany, Ireland, the Netherlands and the UK). In each country at least five, and in some cases more than ten, interviews were conducted to gain a range of perspectives (including those of government health policy, a regulatory agency and a laboratory service). Where possible, multiple interviews were sought from each perspective. See Annex 1 for details of interview sampling.

1.1.6 Patent analysis

Every patent held by the firms identified from the internet, directory and press release sources as being involved in PGx was analysed. This means that all patents for small companies were reviewed. Patents of large companies after 1995 were reviewed. This method was used in preference to searches for sets of keywords due to the difficulty of undertaking Boolean searches on the USPTO website and the slow interface speed.

1.1.7 E-mail survey

In order to understand the range and extent of factors influencing clinical implementation of HER2 and TPMT testing, an e-mail survey targeted

Table 1-1: Organisations interviewed

Company	Country	Sector
Abbot Laboratories	USA	Large Pharma
Astra Zeneca	UK	Large Pharma
Biocenter Basel	Switzerland	Research Institution
DakoCytomation Denmark A/S	Denmark	Diagnostic/Bio-Pharma
Dr. Margarete-Fischer-Bosch-Institut für Klinische Pharmakologie	Germany	Research Institution
DxS Ltd	UK	Service
Epidauros Biotechnology AG	Germany	Service
F.Hoffmann-La Roche AG	Switzerland	Large Pharma
Genaissance Pharmaceuticals	USA	Diagnostic/Service
Glaxo SmithKline	UK	Large Pharma
ICON plc	USA	Contract Research Org.
Institut für Pharmakologie, Kiel	Germany	Research Institution
Karolinska Institute	Sweden	Research Institution
Millennium Pharmaceuticals Inc.	USA	Bio-Pharma
Novartis Pharma AG	Switzerland	Large Pharma
Pfizer Research	UK	Large Pharma
Sanofi-Aventis (former Aventis)	Germany	Large Pharma
Sanofi-Aventis (former Sanofi)	USA	Large Pharma
Schering AG	Germany	Large Pharma
St. Jude Children's Research Hospital	USA	Research Institution
Wyeth Pharmaceuticals	USA	Large Pharma

Grey background: companies

on relevant clinical sites (e.g. oncology and haematology departments, breast cancer clinics and paediatric hospitals) requested information addressing several dimensions of the clinical practice of such tests. This included possible infrastructure, financial, perceptional, educational, social and legal barriers to implementation. The level of implementation within the respondent group was based on consistency of use, measured as the percentage of patients actually tested before they receive treatment.

A mailing list of physicians and heads of departments possibly involved in HER2 or TPMT testing was compiled for the countries targeted by the survey: the UK, Ireland, Germany and the Netherlands. The sample surveyed consisted of 407 physicians from those four countries. The survey attempted to include as many relevant hospitals and clinics as possible in each country, by contacting local networks. The survey was sent out by e-mail. A total of 111 responses were obtained from physicians; some completed the questionnaire, others replied that they do not perform the test. Respondents were asked to complete the questionnaire in their own language or give their view on the topic. They were given two weeks for submission, after which two reminders were sent.

2. Global R&D activities

Public- and private-sector PGx in the EU was mapped, including a comparison of research activities, different forms of technology transfer and framework conditions. Trends that distinguish American and Japanese from European approaches were identified.

2.1 Public sector

The public-sector mapping exercise found 264 research organisations worldwide with a close interest in pharmacogenetics and pharmacogenomics. As illustrated in Figure 2-1, 166 institutions were identified in Europe, 73 in the USA and 25 in Japan. The relatively low number of research groups in the USA could be due to methodological reasons. Firstly, in order to identify PGx research groups, researchers were asked to comment on the lists of groups already identified and to add any missing ones. This iterative process worked only at European level, however, due to the lack of response from US groups. On the other hand, the low number of research groups could reflect their structure, not their activity. As shown by the online survey, research groups in the USA tend to be bigger and, on average, have twice as many researchers as European teams (data not shown).

The study confirmed that PGx research is a field of growing interest. Nearly two thirds of the research groups responding had increased their number of staff, and one third had remained at the same level. Only 3% of all research teams had shed staff.

The survey also showed that PGx is a highly interdisciplinary field. This is reflected in the composition of research groups. In most countries researchers with a biological and a medical background work together. Other scientific

Figure 2-1: PGx research groups worldwide

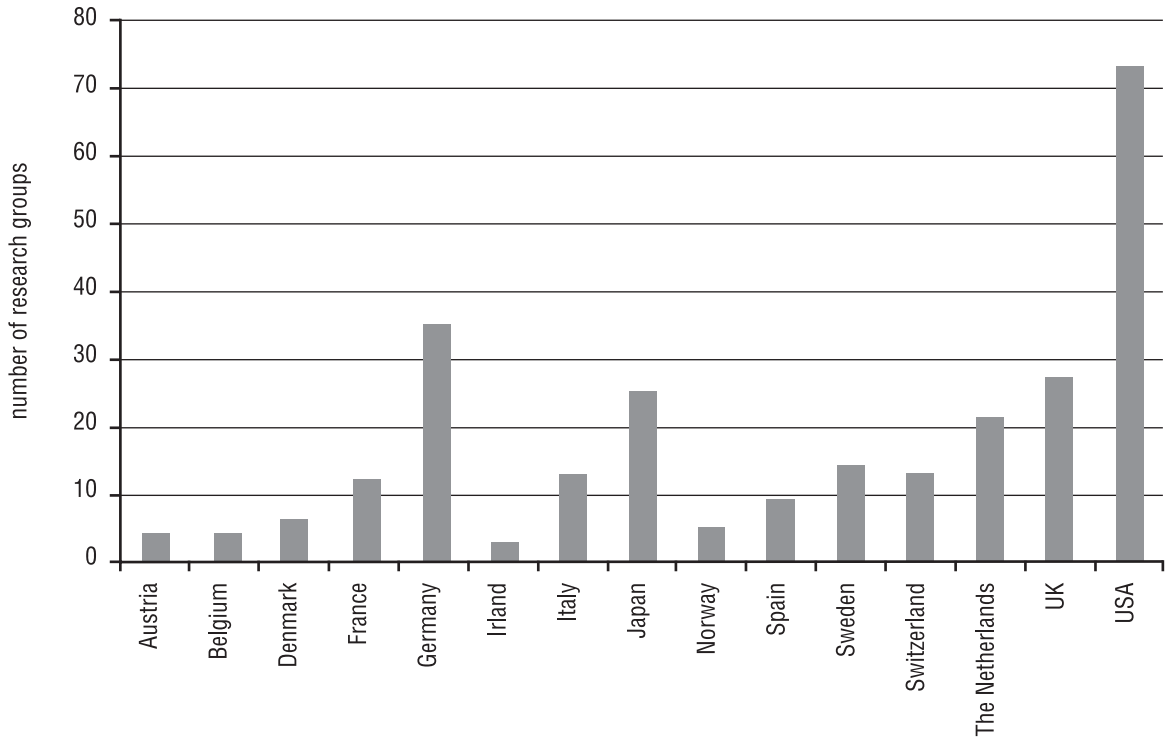
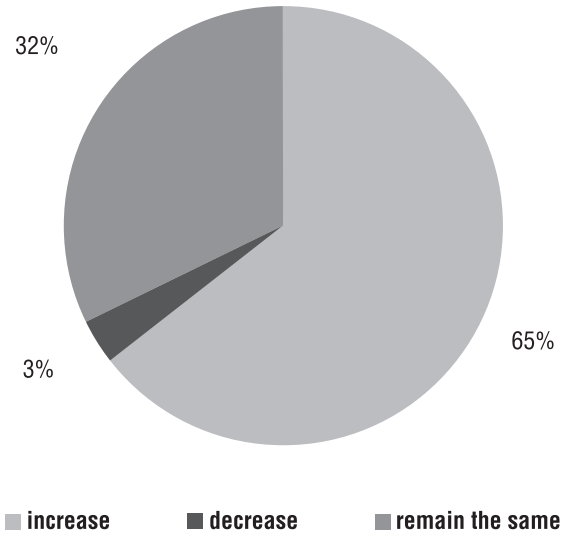


Figure 2-2: Trends in research staff development the last 5 years



backgrounds, such as mathematics/IT, chemistry and pharmacology/pharmacy are represented in only some of the research teams. In Europe, German and UK research groups tend to be more homogeneous rather than to integrate all disciplines. It emerged from the interviews that these groups use publicly available tools more often to deal with mathematical problems and the IT aspects of PGx rather than include these skills in their own research team. This apparent lack of awareness of the interdisciplinarity required in PGx research could cause problems with efficient data analysis.

2.2 Private sector

In order to compile a list of companies active in the field of pharmacogenetics and pharmacogenomics, the private sector was mapped. Initially a total of some 300 firms claiming an interest in PGx were identified from press releases. For example, one firm with a minor interest in PGx (Dakocytomation) was missed. This is probably because none of the company's 28 press releases on NewsAnalyzer included either the term pharmacogenetics or pharmacogenomics. It is highly unlikely that many other companies with PGx activities were missed. All firms were then examined via their company websites and data contained in industry directories. The operational definition of pharmacogenetics was used to identify firms with a genuine interest in this field. This reduced the numbers very considerably to the core group of companies plus another group with a minor interest in the technology. Companies were defined as having an interest in PGx if they had active research or product development programmes relating to the technology. They were not included if they simply discussed the general idea of PGx/personalised medicine as part of their corporate background information, but showed no signs of actively working in the field. Firms were listed as having a minor interest in PGx on the basis of the following criteria only: a) PGx was not the main focus of the company; b) work on PGx constituted only a very small fraction of their overall R&D portfolio; c) at most they had only a single product on the market or under development. By contrast, firms with a major interest in PGx had the technology as a major part of their overall R&D strategy and normally had multiple products on the market or under development.

All core firms were then profiled in detail from primary company documents and websites, including location, age, number of staff, research spending, PGx-related technology and products and services sold/under development. Their products and services were also classified in relation to the technological options identified, enabling comparison between firms and more detailed analysis of the development of particular groups of technologies. All PGx-related collaboration was identified from company documents/websites, ReCap.com and a search of NewsAnalyzer. Each case was then validated one by one. Data on the investment made by large firms in PGx were derived from the pattern and focus of their external research collaboration.

The private-sector mapping revealed highly dynamic behaviour in terms of number of companies. In the course of the project the number of companies with PGx as their core activity declined continuously. This was due to insolvency

Table 2-1: Firms that were involved in PGx in 2002

Acadia	USA	Disinvested
Clingenix	USA	Ceased trading
DiaDexus	USA	Disinvested
DNA Sciences	USA	Acquired by Genaissance. Still working on PGx
Genome Therapeutics	USA	Merged (Oscient Pharmaceuticals). Disinvested
Incyte	USA	Disinvested
NuTec	USA	Ceased trading
Orchid	USA	Disinvested
Phase-1	USA	Ceased trading
SignalGene	Can	Ceased trading
Structural Bioinformatics	USA	Merged (Cengent Therapeutics). Disinvested
Variagenics	USA	Acquired to form Nuvelo. Disinvested
Visible Genetics	USA	Acquired by Bayer. Still working on PGx
GaiFar	Ger	Ceased trading
Gemini Genomics	UK	Acquired by Sequenom. Disinvested.
HiberGen	Ire	Ceased trading
Oxagen	UK	Disinvested
Sciona	UK	Disinvested

of companies, mergers and strategic repositioning of companies to other lines of business. It is also interesting to compare the recent data with an earlier survey and mapping exercise conducted in 2002. One of the most striking features is the high attrition rate, with 18 firms (approximately 40% of the total) which had been in the core PGx universe (excluding tools, kit and software) in 2002 no longer active in this field (see Table 2-1). Out of these, one (DNA Sciences) had been acquired by another firm listed in the core universe and one (Visible Genetics) by a large pharmaceutical company, six had ceased trading altogether, six had disinvested from the technology, with no evidence of work on PGx in any of their public documents, and another four had been acquired by other biotechnology firms. Of this final group, none listed current R&D programmes on PGx in its public documents.

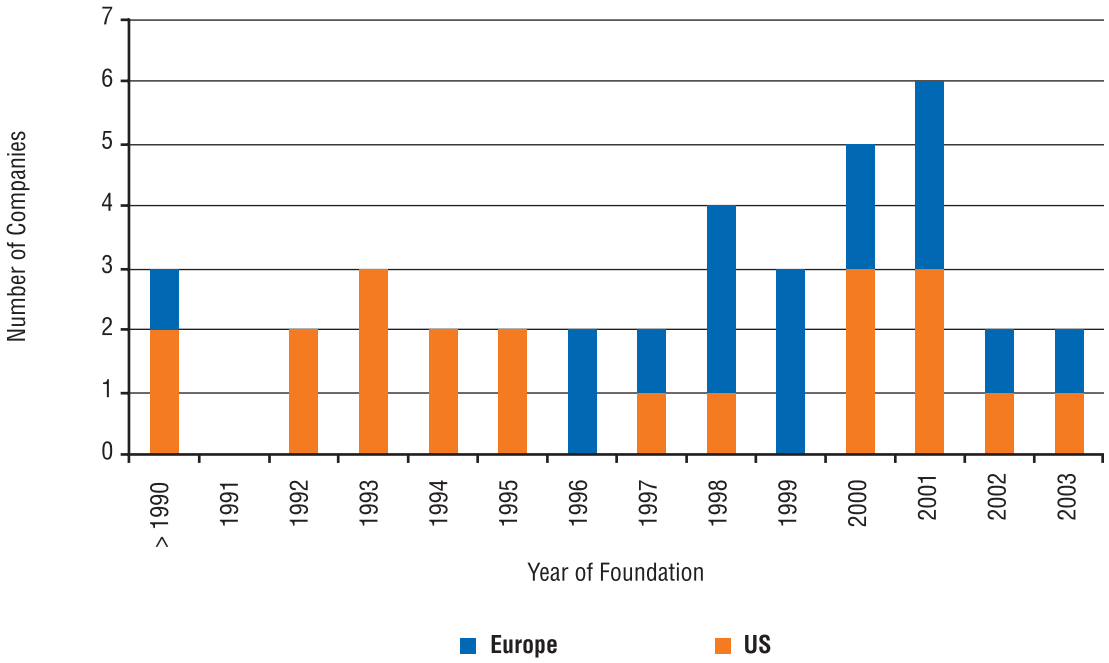
It is difficult to obtain data on the large pharmaceutical companies working on pharmacogenetics due to issues of commercial confidentiality. Some details of their activities are discussed below, but the main focus of this analysis is on the small and medium-sized enterprises (SMEs), for which information is available.

As described earlier, the pharmacogenetics industry was broken down into a core universe of 47 SMEs with a significant interest in developing the technology and a further 18 SMEs with a minor interest in this area (see Annex 1 for tables providing full details of all the 47 firms in the core group, including their location, size, age and technology focus. Annex 2 summarises the investment being made in PGx by firms with a minor interest).

The main firms are split roughly 60/40 between North America (29 firms) and Europe (18), with five UK firms, three German and two French. The oldest public core PGx companies in the USA are Interleukin Genetics (founded in 1986) and Genelex Corp (1987). The oldest public core PGx company in Europe is Dakocytomation (founded in 1966). The early '90s saw a number of start-ups in the USA, and from 1996 on strong activity can be observed in Europe (Figure 2-3).

Out of the core group, 19 are focusing solely on developing PGx diagnostic tests, nine are both developing diagnostics and supporting drug development, either in-house or in partnerships with other companies, 11 are involved in providing

Figure 2-3: Public PGx companies: start-ups in Europe and the USA



PGx-related support services and another eight are producing specialist tools, kits and software. Only a relatively small proportion of these (19 or 40% of the 47 firms in the core universe) can be described as dedicated pharmacogenetics companies. This illustrates the fact that PGx is often only one of a number of commercial activities being undertaken by these companies. For example, several companies in the group working on both diagnostics and drug development are relatively large and well-established biotechnology and genomics firms involved in drug discovery and development (e.g. Curagen, Millennium, deCODE and Genset). The same is true of firms working only on diagnostics, with several large diagnostic companies involved in nucleic acid testing investing in PGx (Celera Diagnostics, Axis-Shield, Dakocytomation and LGC). By contrast, the bulk of the firms providing PGx services, such as genotyping, DNA banking, etc., are focusing exclusively on this area (Table 2-2).

Out of the 19 dedicated PGx firms all but one (ViroLogic) were started up between 1997 and 2004, four are public companies (Genaissance, DNAPrint Genomics, ViroLogic and The Brain Resource Company) and most are small, with only three (Genaissance, ViroLogic and Epigenomics) having more than 100 staff.

Moreover, another four firms still in the core universe (Curagen, Millennium, ExonHit and Genset) have significantly reduced their investment in the technology. However, during the same period another 19 firms joined the core universe, leaving the total size of the PGx sector virtually unchanged.

The relatively small total number of firms in the core universe, the lack of a large group of dedicated PGx companies and the high attrition rate and signs of disinvestment by incumbents highlight the lack of a well-developed market for PGx and the problem of establishing a commercially viable business model for the technology. Most companies see PGx as an additional tool in the drug development toolbox. Their intention is to broaden their approach to "personalised medicine" which is technically wider than PGx (products). Only diagnostic companies see a pure market for PGx products. Despite this, the field is continuing to attract commercial interest, as demonstrated by the significant number of new firms that have been created to work on PGx in the last three years.

Table 2-2: Core universe of firms working on PGx

North American firms		European/other firms	
PGx drug development & diagnostics (5)		***PGx drug development & diagnostics (4)***	
Curagen	USA	Astex Technology	UK
Egeen	USA	deCODE/Encode	Ice
Genaissance (DNA Sciences)	USA	Epidauros	Ger
Millennium	USA	Genset (part of Serono)	Fra
Myriad Genetics	USA		
Diagnostics only (11)		***Diagnostics only (8)***	
Celera Diagnostics	USA	Axis-Shield	UK/Nor
DNAPrint Genomics	USA	Dakocytomation	Den
Genelex	USA	Epigenomics AG	Ger
Genomas	USA	Ipsogen	Fra
Genomics Health	USA	Jurilab	Fin
Gentris	USA	LGC	UK
Interleukin Genetics	USA	TheraStrat	Switz
Prediction Sciences	USA	Vita Genomics	Taiw
Prometheus Laboratories	USA		
Third Wave	USA		
ViroLogic	USA		
PGx services (incl. samples) (7)		***PGx services (incl. samples) (4)***	
First Genetic Trust	USA	The Brain Resource Company	Aust
Gene Logic	USA	CXR	UK
Genizon Biosciences (Galileo Genomics)	Can	DxS	UK
Genomics Collaborative	USA	Medigenomix	Ger
Pergelen Sciences	USA		
Seryx	USA		
Viral Therapeutics	USA		
PGx tools, kits and software (6)		***PGx tools, kits and software (2)***	
Affymetrix	USA	Amersham Biosciences	UK
Golden Helix	USA	Biotage	Swe
Nanogen	USA		
Sequenom	USA		
Tm Biosciences	Can		
Waban Software	USA		
Firms with a minor interest in PGx			
North American firms		**European/other firms**	
Amgen	USA	AdnaGen	Ger
ARCA Discovery	USA	Exon Hit	Fra
Cardinal Health	USA	GeneScan Europe (cyp chip)	Ger
Ellipsis	Can	HepCgen (viral genotyping)	UK
GeneOhm Sciences	USA	IntegraGen	Fra
InSite Vision	USA	Memorec Biotec	Ger
NeoPharm	USA	PharmaMar	Spain
Panacea Pharmaceuticals	USA	Solvo Biotechnology	Hungary
PolyGenyx	USA		
TriPath Imaging	USA		

It is difficult to measure large companies' level of interest in PGx directly, as few companies give details of their in-house programmes on their websites. Therefore a number of indirect means were used to assess large companies' activity in this area, including analysing large companies' collaboration in PGx and their patenting activity. Table 2-3 contains an overview of the total number of alliances and patents in the field of PGx. A total of 32 large companies were involved in 113 (41%) of the 273 PGx alliances. These were split between development of in-house capabilities through acquisition of equipment and services (27), application of PGx to drug discovery and development (63) and development of diagnostics (23).

In terms of intellectual property, only 13 of the 26 EU/US companies listed in Table 2-3 held

Table 2-3: Large firms investing in PGx

Firm	Location	Total alliances (1997-2004)	No of patents
US companies	**(13)**	**(48)**	**(24)**
Abbott Laboratories	USA	3	15
Amgen	USA	1	2
Biogen	USA	4	0
Bristol-Myers Squibb	USA	8	2
Genzyme	USA	1	-
J&J (Janssen)	USA	1	0
Lilly	USA	3	0
Merck	USA	4	2
Millennium	USA	3	-
Pfizer (Pharmacia/Parke-Davis/Warner Lambert)	USA	15	1
Proctor and Gamble	USA	1	-
Schering Plough	USA	1	0
Wyeth	USA	3	2
EU companies	**(13)**	**(54)**	**(20)**
AstraZeneca	UK/Swe	8	1
Aventis (RPR)	Fra/Ger	6	0
Bayer	Ger	7	2
bioMerieux–Pierre Fabre	Fra	1	-
Boehringer Ingelheim	Ger/Aus	2	2
Ferring	Swe	1	-
Glaxo SmithKline	UK	16	1
Novartis	Switz	2	4
Novo Nordisk		1	1
Roche (including Roche Diagnostics)	Switz	7	9
Sanofi Syntholabo	Fra	1	0
Schering AG	Ger	1	-
Serono	Switz	1	-
Japanese companies	**(6)**	**(7)**	**(1)**
Fujisawa	Jap	1	0
Ono Pharmaceuticals	Jap	2	0
Sumitomo	Jap	1	1
Daiichi	Jap	1	-
Mitsubishi Pharma	Jap	1	-
Sankyo Pharma	Jap	1	-

Note: Companies making the greatest investment in PGx highlighted in blue. Other companies with significant investment highlighted in yellow.

PGx-related patents (a total of 44 PGx patents were identified). It should also be noted that almost all of these patents are gene-specific and only mention PGx alongside a number of other applications related to diagnosis, prognosis and disease stratification. Consequently, it seems that few companies are conducting in-house research directly on PGx in general and that most pharmaceutical companies have been gaining access to core PGx technology either by purchasing specialist services or through research collaboration. It is notable that the only European company with a significant number of PGx-specific patents is Roche (including Roche Diagnostics), which has IP on the use of a number of drug metabolising enzymes and methods for the detection of polymorphisms. Given the significant number of alliances in which it is already involved (7) and the launch of Amplichip, it can be seen as the leading large European company in this field.

2.2.1 Research areas and targets

In the online survey on PGx, research groups were asked to specify their objectives in terms of basic and applied research. They could choose more than one objective. Public research groups aim at both basic and applied research in nearly equal proportions. Elucidation of basic mechanisms and diagnostic applications account for 24% and 22% of all activities. Pharmaceutical applications combining basic and applied research along the value chain make up another 16% of all activities. Research objectives vary

between countries. Whereas the UK has a strong focus on basic research, German research groups are more often active in the field of validation and standardisation of tests.

The main targets for PGx research by public research groups are the entire population or specific subgroups. The most important target of groups working in this area is selected patient groups. Animal, cell and microbial systems are of less importance in PGx research. Research subjects deal with all types of organs and biological subsystems.

There seem to be some specific national fields of interest. For example, research on lipid metabolism is mainly carried out in the USA, whereas some German and UK research groups focus on research on the immune system and gastrointestinal tract. However, the sample was too small for these hints of special national interests to be considered representative.

For nearly 80% of all the public-sector research groups which answered, SNP analysis is the basic approach of their PGx research. 65% analyse enzymatic activity. This approach aims at elucidation of biomedical questions, as summarised in Table 2-4.

Table 2-4: Biomedical questions addressed by PGx research in the public sector

Biomedical questions	Percentage of answers
Metabolic pathways	52
Disease mechanisms	27
Disease predisposition	27
Inflammation	20
Pathogenesis	17
Immunity	13
Signal transduction	12
Regulatory circuits	5
Apoptosis	3
Regeneration	2

An earlier study by Martin *et al.* [8] mapped the main technological options for the commercial development of pharmacogenetics (PGx) [9, 10]. These can be divided into 12 options under six broad headings related to the discovery and development of new medicines and to the prescription and marketing of therapies already licensed:

- Drug discovery;
- Safety of drugs under development;
- Efficacy of drugs under development;
- Safety of licensed drugs;
- Efficacy of licensed drugs;
- Stratification of diseases and infectious agents into sub-types.

As PGx offers services at all stages of drug discovery and development, companies have interests in the various links along the value chain of the pharmaceutical innovation process.

The synopsis of the main technological options that each firm is working on provides an analytical framework for examining which technological options are currently of greatest commercial interest. Although it is a crude indicator, the number of firms working on a given option provides a useful idea of its prospects of being successfully developed in the near term, as options attracting little investment stand little chance of being introduced.

These data are summarised in Annex 3 and point to a number of key conclusions:

a. Commercial interest in pharmacogenetics is spread across the whole process of drug discovery and development. However, the vast majority of interest is concentrated on just seven of these options, with little commercial investment in drug rescue (either safety or efficacy), market extension strategies, post-marketing surveillance or the use of efficacy data in marketing existing drugs.

b. Most investment is being made in services and products supporting pre-clinical and clinical drug development. This is followed by the development of diagnostic tests as an aid to prescribing and to enable disease stratification for drugs developed. A smaller

number of firms are also providing services to support drug discovery.

c. Firms supporting the application of PGx to clinical drug development are focused on both safety and efficacy. They are offering a range of services (including Absorption, Distribution, Metabolisation and Excretion (ADME) testing, toxicity screening, genotyping and association studies) and products (genetic tests for ADRs, ADME/CYP450 assays and chips, database of ADRs and software tools). These are being sold predominantly to large integrated pharmaceutical firms.

d. Firms developing technologies to support pre-prescription genotyping are almost entirely focused on developing diagnostic tests as distinct products, rather than selling services. Almost all of these firms are dedicated diagnostic companies, with only a few also working on drug development (Genaissance, Egeen, deCODE). Most interest is being shown in developing efficacy tests (16 firms), with slightly less support for safety testing (11 firms) and disease stratification (10 firms).

e. The small group of firms supporting drug discovery mainly provide support services to large pharmaceutical companies with the emphasis on ADME, CYP450 and toxicity analysis and testing.

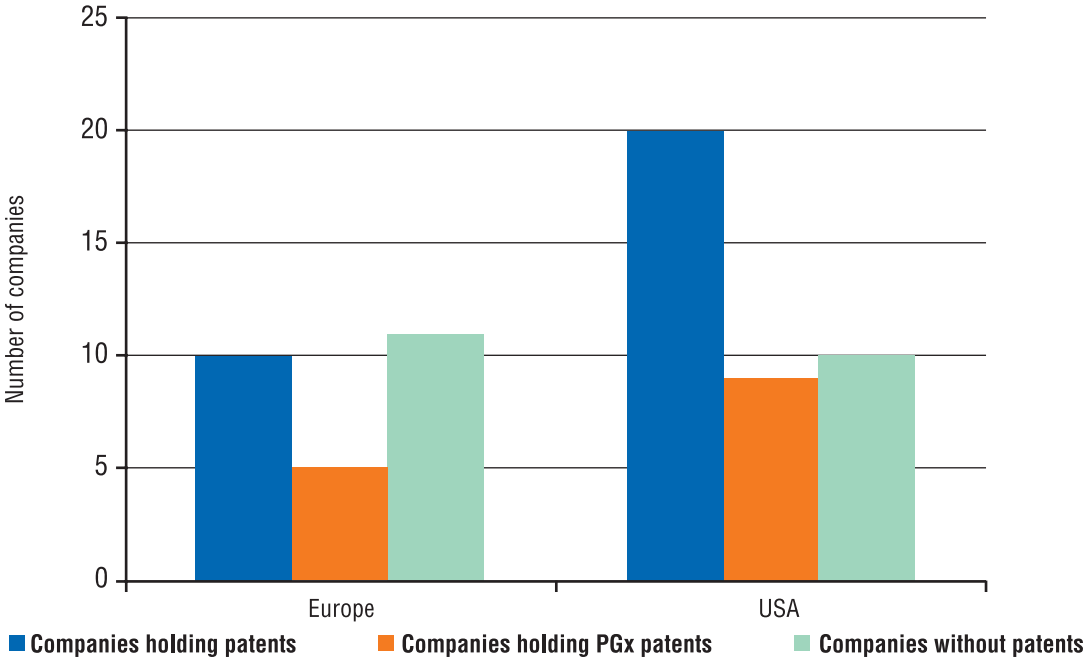
2.2.2 PGx products in the pipeline

As described earlier, PGx applications can be analysed from two perspectives. On the one hand, PGx is seen as a tool in the drug development toolbox. In this respect PGx applications will not be products in their own right but a method to develop new drugs. This approach is seen as one step further towards "personalised medicine". On the other hand PGx applications will lead to new tests and test kits that will be products for the diagnostic industry.

In order to gain insights into upcoming products and developments in the private sector, a patent analysis was carried out, as described in the "Methodology" section. Only 50% of the companies identified as core PGx companies, based on their research activities and their own presentation, hold PGx-related patents. One in two PGx companies hold no patent (see Figure 2-4).

Patents do not directly indicate new products but rather research areas. Hot spots of activities

Figure 2-4: Number of core PGx companies holding patents



are various cancer indications, cardiovascular disease, obesity, diabetes and asthma.

To add to the patent analysis, respondents from the private sector were asked to predict future PGx products. Most companies were unable to answer this specifically. However, there was general agreement that the main early test would be in oncology due to the greater ability to characterise samples from which PGx data and therefore genetic markers could be defined. Also, many current drugs have poor efficacy and thus the potential for major improvements is very high. One respondent stated that there was a good chance to close the PGx/diagnostics linkage in this area. Another saw inflammation and autoimmune diseases as a second area for products in the near future. Nevertheless, experts were sceptical about the time-scale for PGx products. Some respondents considered 3 to 5 years realistic for PGx-related oncological products, whereas others stated that, even in such an advanced sector as oncology, products are "not around the corner".

By contrast, experts were more precise about the diagnostics sector, where the relevant companies forecast a huge number of different tests for the near future. As an estimated 35 million molecular diagnostic tests were carried out in hospitals and laboratories in the USA in 2003, a large market already exists. This is forecast nearly to double to 67 million tests per annum by 2009 [11]. Infectious disease testing and blood banking applications are leading the way at present, but pharmacogenetic predisposition diagnostics and molecular cancer diagnostics applications will follow soon [11]. At present the molecular diagnostic PCR segment is divided into four areas of customer interest:

- Academic (45%);
- Pharma (25%);
- Biotechnology (10%);
- Clinical (20%).

In all, some 49 tests are either in use or under development. Of these, just over half (26) are already available for some kind of experimental or clinical application. However, relatively few have formal regulatory approval. Furthermore, the extent to which they are used in practice is very difficult to assess, as some tests that are available have been developed purely as "proof of concept" diagnostics and are not likely to be marketed as commercial products. These data are summarised in Table 2-5.

Details of all diagnostic products currently offered for some kind of research or clinical use and of all new tests under development by the firms in the PGx universe (including firms with a minor interest) are given in Annexes 4 and 5. It is difficult to draw a clear distinction between general services offered, discreet tests and stand-alone products. The data in Annex 4 therefore include some tests that might only be available in a particular company's laboratory. The tests described in Annexes 4 and 5 can be classified under five broad headings:

1. PGx tests for drug metabolism

The main group of established tests are for drug metabolising enzymes (DMEs – mainly

Table 2-5: Commercial PGx tests available for use or under development

	In use			Under development			All
Type of test	**US tests**	**EU/other tests**	**Total**	**US tests**	**EU/other tests**	**Total**	**Total**
Drug metabolism	6	8	14	1	0	1	15
Anti-viral drug resistance	4	1	5	2	1	3	8
Cancer (disease stratification)	2	3	5	3	3	6	11
Other conditions	3	1	4	8	3	11	15
TOTAL	14	12	26	14	7	21	49

NB: This includes the two products produced by big pharma (Bayer's HIV genotyping test acquired via Visible Genetics and Roche's AmpliChip).

Cytochrome P450 alleles), which are being sold on the two main markets mentioned earlier: studies of drug metabolism during pre-clinical and clinical drug development, and pre-prescription patient testing. They are offered in a number of different forms, including in-house laboratory testing, assays and kits for use in third-party laboratories, DNA microarrays (chips) for use in point-of-care diagnostics, and even direct-to-consumer testing services (Genelex). The growing number of chip-based diagnostics is a significant development, as this technology offers the possibility of lower-cost/higher throughput analysis in the longer term. There is only one commercial provider of DNA-based TPMT testing, largely due to a patent on it (licensed by Prometheus Laboratories from Genaissance). In addition to these tests offered by firms in the core PGx universe, Roche recently launched its AmpliChip as a technology platform for PGx and related testing. The first application is CYP450 testing.

In terms of tests under development for DMEs, it is notable that only one additional firm (Gentris) is looking to enter this market. This probably reflects the relatively large number of established providers of these products and services, and the presence/entry of large incumbent diagnostics firms (Amersham, Roche), which have strong marketing capabilities.

2. Anti-viral drug resistance testing

Another group of relatively well-established PGx tests are for viral genotyping, in order to identify anti-viral drug resistant sub-types as a means of guiding therapy. Assays and test kits are currently marketed for both HIV and hepatitis C (HCV) and are also under development for hepatitis B. In addition to the tests produced by the firms in the core universe, Bayer is marketing a test for HIV drug response following its acquisition of Visible Genetics.

3. Cancer PGx testing (disease stratification)

One of the areas attracting increasing attention is the possibility of using somatic genetic profiling of tumours as a means of stratifying cancers into sub-types based on their response to new and existing chemotherapies. The tests offered by Genomic Health and Myriad and those under development by DNAPrint Genomics, Epigenomics and Ipsogen are largely aimed at improving the use of established drugs, such as Taxol, Tamoxifen and Carboplatin. By contrast, the tests offered by Dakocytomation and Ipsogen and those under development by ViroLogic and DxS are designed to guide development and use of the new generation of "targeted" cancer therapies, including Herceptin, Glivec, Iressa and other drugs aimed at the EGFR gene product.

4. PGx tests for other diseases

A number of other PGx tests are also available. These include tests to guide the use of albuterol therapy (asthma) and drugs to treat rheumatoid arthritis (RA) and glaucoma. In addition, Genaissance has created a test to assess an individual's risk of contracting Long-QT syndrome. There are also a relatively large number of tests under development for drugs to treat important common conditions, including response to statins (hypertension), clozapine (schizophrenia), SSRIs (depression) and anti-RA drugs. However, many of these are still at an early stage of development.

5. Other applications of PGx

It should be stressed that the main focus of commercial activity amongst the firms in this survey, as opposed to large integrated pharmaceutical companies, is on diagnostic products and services.

The analysis that most PGx applications are in the field of drug development, including clinical studies, was endorsed by experts. This means that the pharmaceutical industry will benefit directly from these products. Physicians and patients will not avail themselves of the tests but will benefit only indirectly from innovative drugs.

In contrast to earlier publications [12, 13], companies stated that at present PGx plays no

role in the reinvestigation ("rescue") of failed or recalled drugs and substances.

2.2.3 Major scientific and technical barriers and drivers

With regard to the core technological requirements for PGx, there was a clear consensus amongst most respondents that there are no major technical barriers.

Problems identified include:

- Low availability of samples from well-characterised patients. This is a problem in PGx research, both in terms of availability of such samples and also the ethical issues surrounding the process (see below).
- Lack of clear evidence to relate drug response to genetic status. This is the critical link and has been defined for only very few cases to date.
- In terms of access to technology, the process of identifying and negotiating rights to patents on DNA with a diverse group of owners is a major "nuisance" to some respondents.
- The high cost of PGx work, including the capital and hiring cost of setting up a PGx team, is an obstacle to PGx research. This includes the availability of well-trained human resources (e.g. in the field of bioinformatics). PGx can add a high level of complexity (sampling, data management, etc.) to a clinical study which has not yet been proven to be justified. The cost of genotyping can be very high and can be prohibitive.
- The bioinformatics systems are not yet adequate to cope with the huge volumes of data. Data "integration rather than interpretation" remains the challenge according to some respondents. Also, organising data collection is a problem in terms of collecting only the data for the ongoing study that has ethical approval, as "off-the-shelf" arrays will often collect data on other parameters. However, to devise customised arrays for every trial is too expensive.
- Some respondents stated that instrumentation and methodologies used in PGx are new and require further development. However, this opinion was not shared by all respondents.
- The actions of ethical committees pose a major barrier to PGx research. Moreover large clinical trials may need to include patients from several states, which in the EU adds an additional level of complexity due to lack of harmonisation of ethical requirements (see Chapter 4).
- Diverse practices related to data protection at MS level are perceived to pose a significant barrier to research.

Respondents from the public sector mostly agreed to the barriers mentioned by the private-sector experts (see above). From their point of view an additional major barrier to PGx research is the limited access to private-sector databases. In their opinion companies' genetic sample databases would offer a huge chance for linking genetic markers with disease. Access to the industry's PGx trial information could stimulate research enormously [14]. This should be promoted by appropriate European funding programmes (see section on "Framework conditions" for details).

Companies' PGx activities are mainly science-driven rather than market-driven. Some of the companies surveyed were founded directly by scientists who saw a technical opportunity in this field. However, most companies gradually built up PGx in-house as an area of activity. In some cases this arose due to the emergence of PGx knowledge amongst the technical staff. In some large companies the strategic decision to integrate PGx into the companies' portfolio was made by the board of directors against the background of lack of innovative products. In this case, the companies mostly followed a platform strategy that did not start with a separate PGx department but with a group of people with different professional backgrounds from various departments (e.g. basic research, clinical research, medical affairs,

etc.). This working group had to identify project families within the company and carry out several projects, recruiting personnel on a project basis. This approach guaranteed acceptance of the new research area and direct integration into ongoing research activities.

Although it has been shown that there was a strong technological push towards PGx activities, the regulatory impetus should not be neglected. As stated by some respondents, the activities of the FDA were an important signal to initiate and integrate PGx research into companies' strategic research planning (see Chapter 4).

2.3 Interaction between academia and industry

One joint call from the experts at the IPTS Workshop in March 2004 was to improve the relationship between industry and academia and to increase public-private partnerships. According to the experts, it is not a matter of just more research but of more coordinated research in the field of PGx, with more interaction between academic and industrial research. Complaints of lack of awareness of what the other side is investigating are frequent, with clear tension between the goals of academic researchers (understanding human genetic variability) and of industry (overcoming this variability). The paradox is that industry has collected and stored the biological samples needed for research but is not necessarily using them, while academics feel that they could make better use of them. A joint call has been made for Commission research programmes to tackle this problem, and it was agreed that it is not a matter of funding but of linking these separate sectors and increasing collaboration between them. This study therefore looked into the current interactions between industry and academia and barriers hampering collaboration between these two sectors.

2.3.1 Numbers and types of collaboration activities

Research into PGx requires the involvement of many different disciplines that are not all present in a single typical research group. Collaboration is therefore necessary to achieve this essential interdisciplinarity. The online survey of research groups revealed a high number of collaboration activities between research organisations (RO) (66% of all collaboration). Industrial collaboration, both with small and medium-sized enterprises (SME) and with large enterprises (LE)

Figure 2-5: Number of cooperation projects in 2003

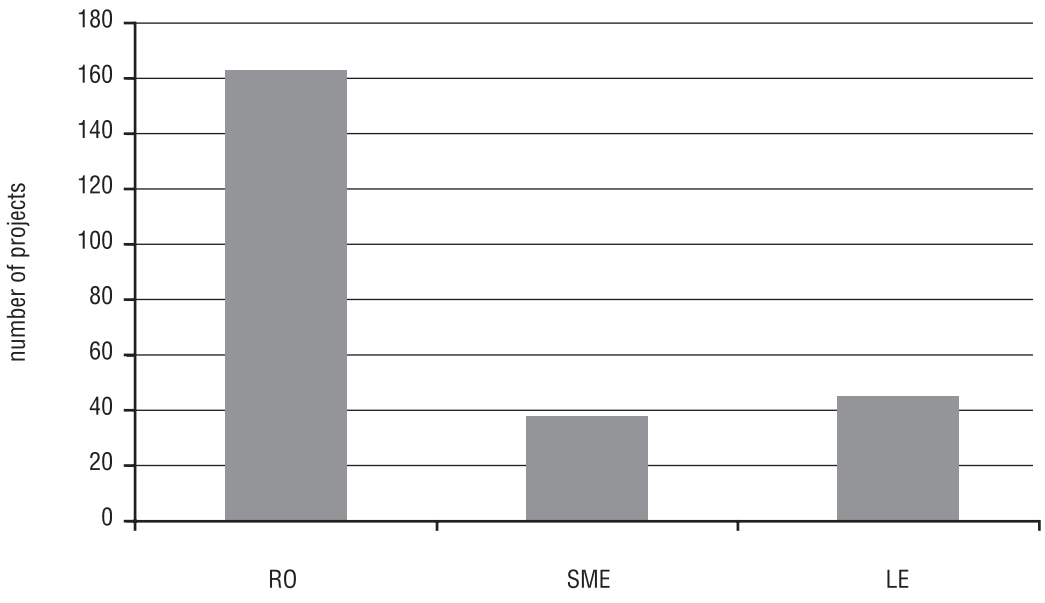
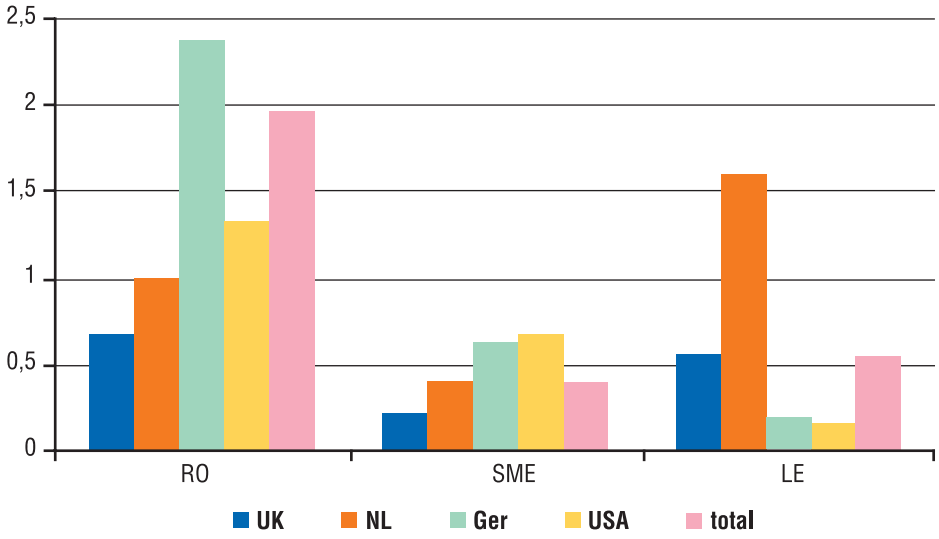


Figure 2-6: National relevance of different types of collaboration activities



contributed only a small share (15% and 18% of all collaboration), as illustrated in Figure 2-5.

The relevance of different types of collaboration varies between countries. In Germany each research group is involved, on average, in 2.3 collaboration activities with another research organisation (RO) but only one out of five research groups is cooperating with a large enterprise (LE). Research groups in the Netherlands are engaged in an above-average number of collaboration activities with large enterprises (1.6 per research group). However, these numbers must be taken as evidence of a national trend but not as an absolute and representative figure due to the small sample size (see Figure 2-6).

The origin of the partner institutions is summarised in Figure 2-7. It shows that the majority of German collaboration activities are

Figure 2-7: International perspective of collaboration activities

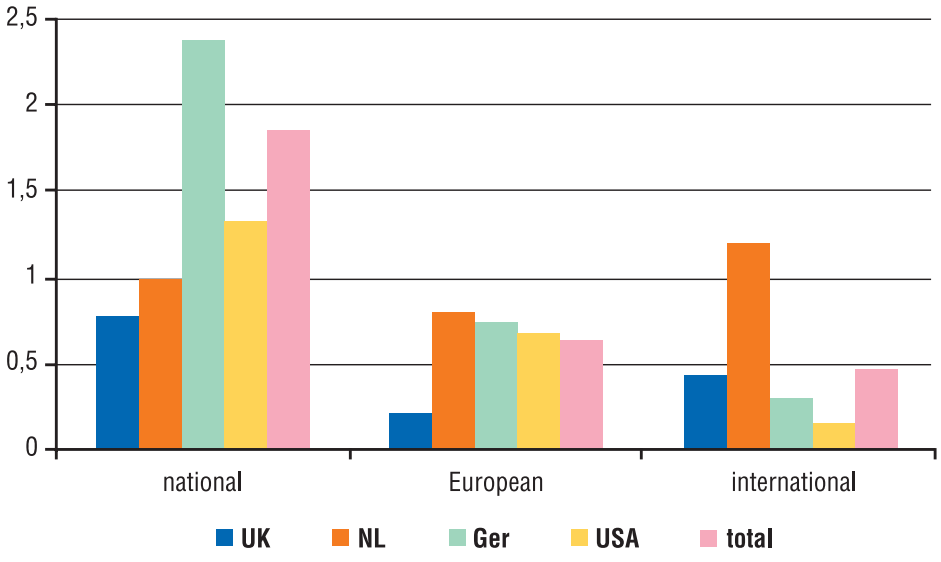
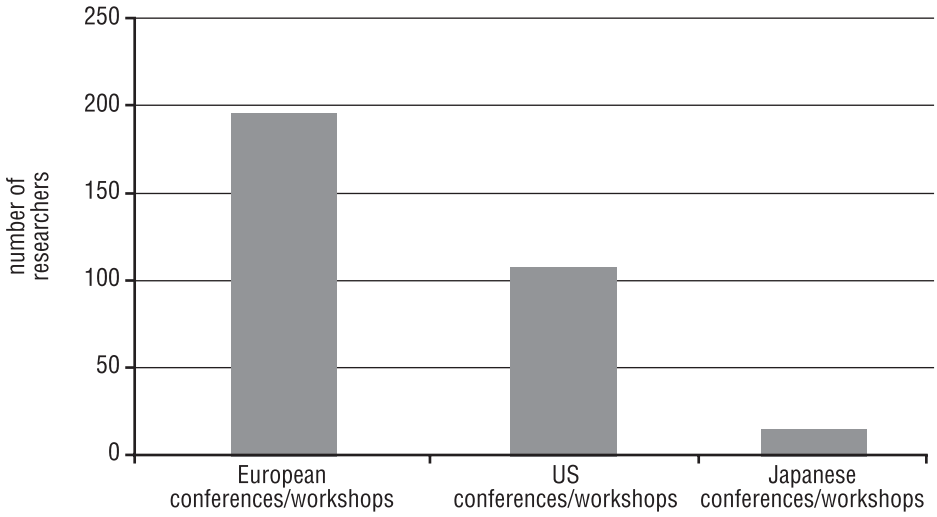


Figure 2-8: Contribution to international scientific exchange in 2003



within Germany. Other countries such as the Netherlands have a more international perspective to collaboration, both European and international (non-European). The survey shows that US research groups have alliances both within the USA and with European partners. This indicates the accepted quality of European research groups as US groups could find good partners in the USA as well (see ranking of research groups).

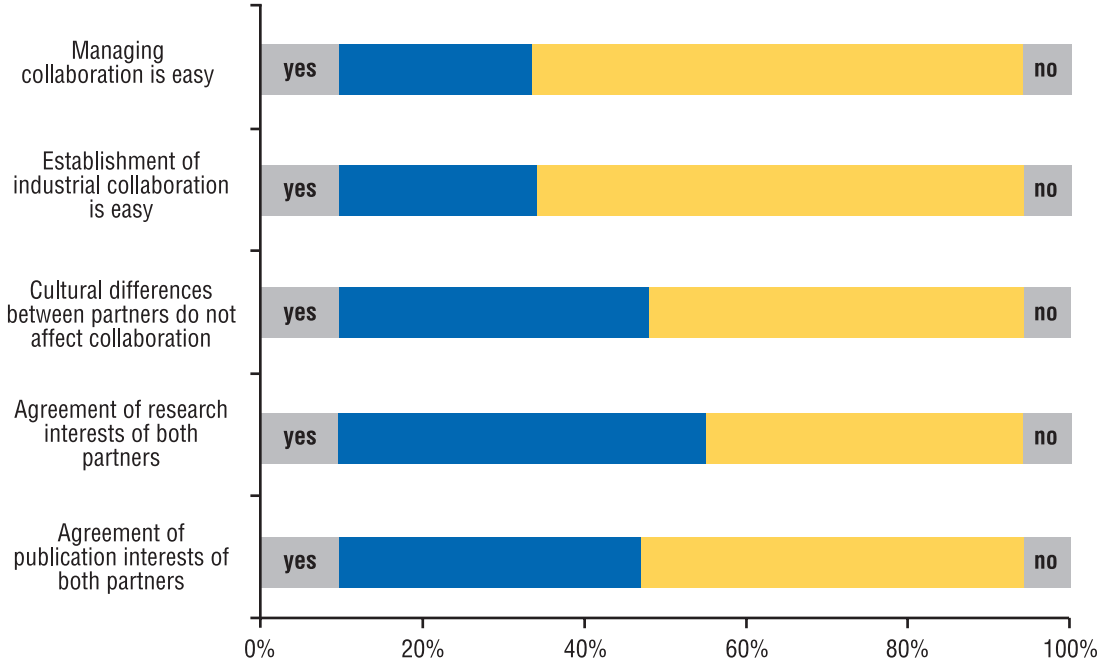
Despite a strong national focus on the part of some research groups, international exchanges are well established and knowledge is transferred through workshops and conferences. Each of the 58 research groups that answered the online survey contributed to the international transfer of scientific knowledge during 2003, with an average of 6.3 researchers attending conferences and workshops (see Figure 2-8).

2.3.2 Management and experience of collaboration

According to interviews with experts from the private and public sectors, cooperation is organised mainly at project level. Research groups conclude a contract with a company to fulfil a particular well-defined task such as development of a specific test or collection of data within a clinical study. It is difficult to establish collaboration going beyond this. The online survey showed that establishment and management of industrial collaboration are perceived as difficult by two thirds of all research groups. Cultural differences and different research and publication interests pose problems for approximately 50% of all research groups (see Figure 2-9).

In general, the private sector values collaboration with the public sector. However, for strategic and confidentiality reasons, only a small proportion of tasks can be subcontracted to the public sector, as explained by one industrial respondent. According to experts from academia, the different research interests are one of the main obstacles to extension of industrial collaboration: industry appears to be mainly product-oriented following a blockbuster strategy that sees PGx merely as a tool to make drug development more efficient. Efforts are made on PGx only if it can help to rescue a drug. Contrary to the opinion of the public sector, representatives of industry complain about problems with IPR matters in public-private collaboration and a lack of awareness of milestone agreements. Thirdly, company representatives criticise high administrative barriers at public research organisations. One expert from the private sector described the difference in research interests by the following generalisation:

Figure 2-9: Experience of industrial involvement from the academic point of view



"Academia is generally concerned about genetic links with disease whereas industry is concerned with genetic relevance to therapy".

Another difference is the scale of research. Academic circles are only able to tackle genome and PGx issues on a small scale, whereas industrial drug development processes require large integrated projects, which can cover the genomic complexity. This explains why the private sector cooperates with the public sector on the discovery aspects and for development of methods.

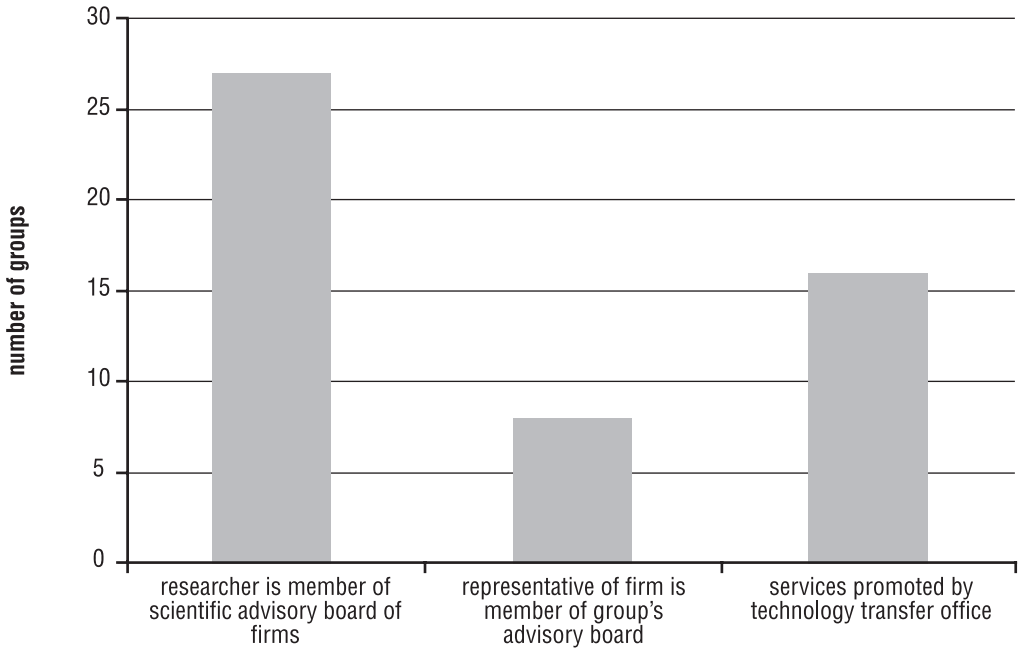
One respondent compared his experience with UK and German university administrations and concluded that German universities still lose a considerable number of potential collaboration projects due to their inflexible administration. Apart from the inflexible administration, the lack of standardisation (GLP, GCP status) of public institutions is an obstacle to industry-academia collaboration.

Alongside project-based cooperation, knowledge transfer between the public and private sectors is organised via persons and technology transfer offices. In nearly 50% of all research groups, researchers are also members of the advisory board of companies. Technology transfer offices promote knowledge transfer in one third of all research groups (see Figure 2-10**).**

In the USA and Japan the establishment of consortia forms a third pillar for networking and knowledge transfer. In July 2003 the Japan Pharmacogenomics Consortium (JPGC) was established to promote the development of infrastructure and national standardisation for conducting pharmacogenomics-related clinical trials in Japan. Its goal is to strengthen the international competitiveness of the pharmaceutical industry in Japan and respond to the ever-advancing need for personalised medicine. Part of this is the urgent development of a platform for conducting clinical trials involving gene analysis, including post-marketing (phase IV) clinical trials. Through JPGC, pharmaceutical firms will be able to collaborate in solving pharmacogenomic trial issues and to develop the required know-how in synergy (DxS 2005).

The NIH initiated a major pharmacogenetics project with funding totalling over US$ 200 million to establish multi-disciplinary research groups. Research groups within the NIH Pharmacogenetics Research Network (PGRN)

Figure 2-10: Strategies for knowledge transfer



were united by the purpose of developing and populating a public database, which was envisioned as a tool for all researchers in this field. Funding of these awards began in 2000 and 2001. The researchers are "driven by the science", and in 2003 outside consultants recommended that the network should strive to become "more than the sum of the parts". The goals of the PGRN are:

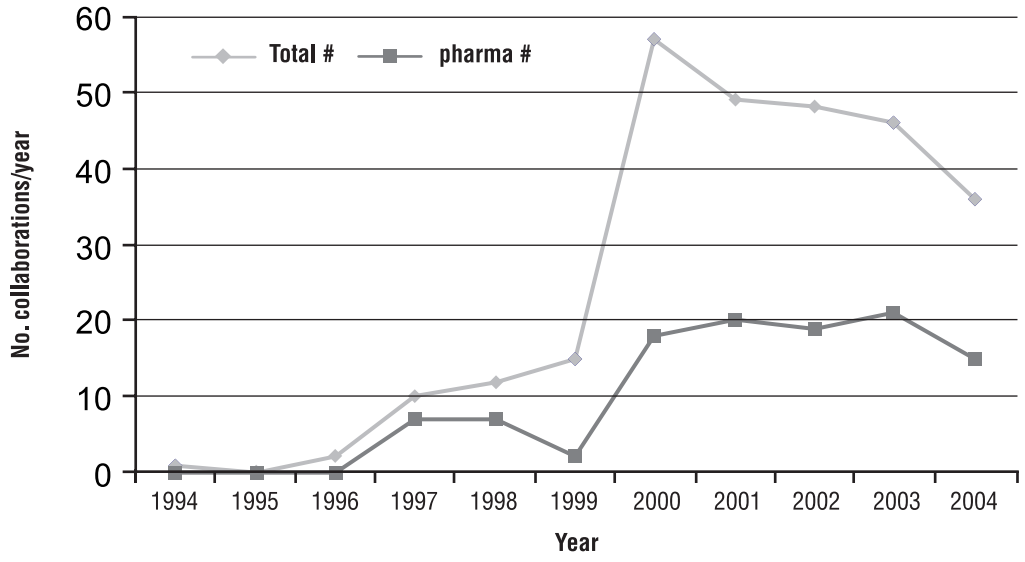
- to perform the highest quality research studies to correlate drug response phenotypes with genetic variation;
- to create a valuable knowledge base (PharmGKB)[16] populated with reliable, searchable and annotated information that links phenotypes to genotypes;
- to become an interactive network of researchers that has an impact on and upgrades the field of pharmacogenetics with knowledge, tools and resources.

Researchers from the Pharmacogenetics Research Network are now trying to start collaboration with European institutions. One of the experts argued that this global alliance can be expected to give an additional knowledge and technology push.

Knowledge transfer into the clinic remains difficult. According to respondents from both the public and private sectors, one major problem hampering acceptance and dissemination of PGx in hospitals is the lack of adequate knowledge among doctors. Health professionals trained before the early '90s lack this knowledge completely. Though genetic background knowledge was integrated into the curricula in the '90s clinicians still feel uncomfortable with interpretation of PGx data. Company experts hope to overcome this obstacle by automated analysers which are easy to handle and produce results which do not differ from standard laboratory biochemical analyses. Experts from academia, however, admit that, even with automated analysers, decisions about therapy will be more complex. More data will be necessary from prospective studies to allow interpretation of PGx data and to feed expert systems for evidence-based applications of PGx knowledge in clinical practice.

16 The Pharmacogenomics Data Base; http://www.pharmgkb.org.

Figure 2-11:PGx alliances 1994-2004



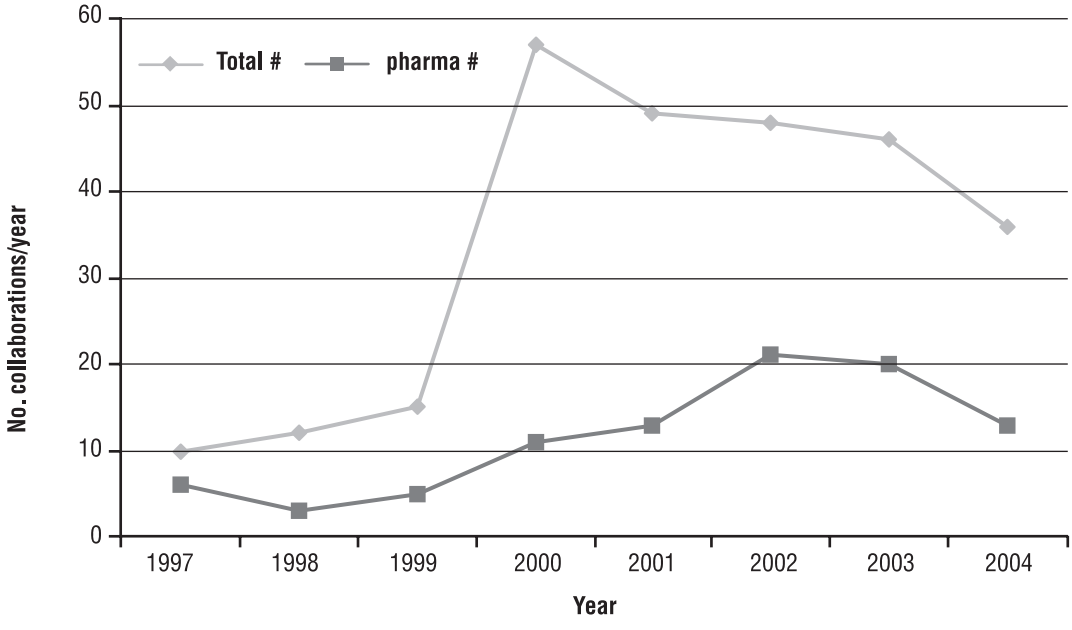
Source: www.recap.com

2.3.3 Industrial collaboration on PGx

The study identified some 273 alliances established in the field of PGx between 1994 and 2004. The growth in the total number of these alliances is shown in Figure 2-11, as is the number of alliances involving large pharmaceutical companies. The year 2000 was marked by rapid expansion of this field, but activity has declined in subsequent years.

Out of the 273 alliances, some 92 (approximately 33% of the total) involved the development of diagnostic products. Figure 2-12

Figure 2-12: Collaboration on diagnostics



Source: www.recap.com.

shows the growth of collaboration in this area, which followed a similar pattern to the general trend. However, only 23 of these 92 alliances involved large pharmaceutical companies and just 13 were with large diagnostic companies, three of which (Roche Diagnostics, Quest and Becton Dickinson) accounted for nine of the alliances. The pharmaceutical companies with the most alliances on diagnostics were Abbott (2), BMS (3), Boehringer Ingelheim (2), GSK (2), Bayer (3) and Roche (2), although a significant number of these alliances are no longer active. Details on industrial collaboration, including partners, size and tasks are summarised in Annex 6.

2.4 Framework conditions

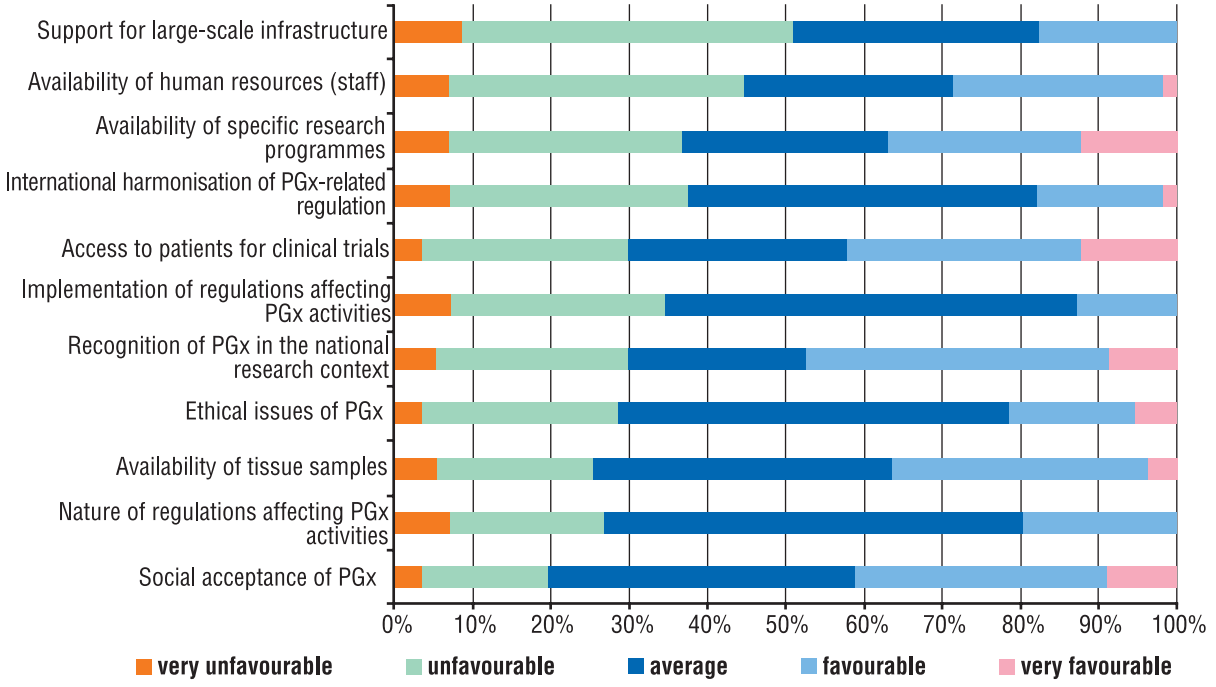
2.4.1 Overall framework conditions

Although 50 years of public PGx research and more than a decade of strategic activities by the private sector have considerably promoted this field, PGx is still not broadly applied in the clinic. One of the reasons for this could be the technical and socio-economic barriers. Scientists from public research groups were asked to evaluate the general framework conditions in the Fraunhofer online survey. In addition, experts from both the public and private sectors were asked to comment on the framework conditions such as regulation, funding, and social acceptance, quality of research and availability of human resources.

The online survey showed that social acceptance and regulations do not affect PGx research in the public sector. Most public researchers stated a pronounced recognition of PGx in the national research context. What is more difficult, as will be discussed in the next chapter, is the lack of availability of adequate funds. Nearly 40% of respondents complained about the lack of specific research programmes. A shortage of human resources hinders efficient research on PGx, a criticism made by every second researcher. Finally, lack of support of the large-scale infrastructure necessary to deal with complex genomic questions is a major obstacle to efficient PGx research (see Figure 2-13).

A similar picture of the non-technical factors influencing PGx investment decisions was painted by the companies interviewed.

Figure 2-13: Evaluation of framework conditions by the scientific community

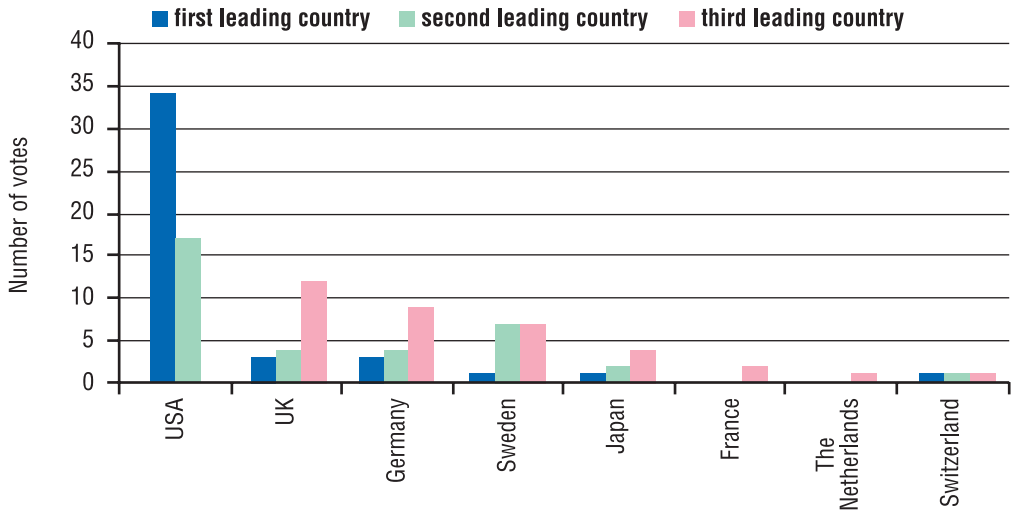


- No company complained about lack of social acceptance. In their experience PGx drugs and PGx tests are well accepted by patients and public. However, some respondents pointed out that in the future the public attitude to availability of genetic data could become a barrier to PGx research. One explained the different perception of genes and genetic data by scientists and the public. Whereas scientists do not think that there is anything special about genetic data, to the public there is still something "mysterious" about them. In order to avoid negative feelings amongst the public and establish transparency, one company initiated an ethical board including laymen (e.g. a representative of a patients' organisation and a lecturer in ethics).
- The quality of public research was not an issue with any company. Research quality (including EU research quality) is regarded as high, although two companies mentioned that the scale is small in relation to the needs. However, industrial respondents said that academia is not involved in genetics applied to therapy, but more in genetics applied to disease mechanisms.
- Availability of human resources is almost no problem for companies. One small company complained about competition from large enterprises that can afford to pay higher wages and thus get hold of the best qualified staff. This problem mainly concerns qualified molecular biologists and clinical pharmacologists with a PGx background.

The evaluation of the scientific quality of research groups gives another view of the adequacy of framework conditions. The research groups were asked to name the leading research institutions and to rank the leading countries in PGx (see Figure 2-14). The result showed a strong lead for the USA, followed by Sweden, the UK and Germany. Several respondents put Japan and Switzerland among the top eight states (votes from research organisations in the same country were not counted). This ranking could reflect the favourable funding conditions in the USA, which were mentioned by several respondents.

Experts described the leading institutions as highly interdisciplinary with a strong link between basic and clinical research, allowing access to patients. A third key to success seems to be a certain critical mass, as experts

Figure 2-14: Leading countries in PGx research



emphasised good infrastructure and support, both technical (e.g. laboratory equipment) and human (e.g. bioinformatic expertise). Although, according to the survey, five of the top seven institutes are US-based, experts from the private sector stated that it was easier to gain access to research and development expertise in the EU.

Regarding the composition of the private sector, some respondents stated that in Europe there is a smaller number of service companies akin to Genaissance than in the USA. This could be a disadvantage for European-based (pharma) companies as the range of services required (analysis, banking, etc.) is not available in Europe.

2.4.2 Regulations

As the first products based on PGx emerge, regulatory considerations will affect drug approval, licensing and delivery long before medicines are prescribed by a physician. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (Geneva, Switzerland), which brings together regulatory officers from Japan, Europe and the USA, has recommended that additional studies be required when drugs are submitted for licensing under a new jurisdiction, in order better to define the clinical characteristics of the drug in the original patient population. One means of addressing this problem would be to institutionalise or quasi-formalise inter-agency coordination of evaluation of genetic variability and drug response, i.e. between the national regulatory agencies such as the UK's MHPRA, Germany's BfArM, the European Agency for the Evaluation of Medicinal Products (EMEA), Japan's Pharmaceutical Affairs Bureau and the Food and Drug Administration (FDA). Exclusively national regulation of new medicines is unlikely to be an adequate means of appraisal in the future [13].

The predominant view in the private sector was that regulatory procedures would be a major factor in defining its activities. However, the procedures were not yet clear. When the final procedures become clear, more pharma will take action to comply.

Industry was happy to obtain clear guidance from the FDA's "Guidance for Industry Pharmacogenomics Data Submission", a draft version of which was published in November 2003 followed by the final version on 22 March 2005. The guidance is intended to facilitate use of pharmacogenomics data in drug development and should help to avoid uncertainties about how PGx data will be used by the FDA in the review process for drug applications. This should encourage open and public sharing of data and information on PGx test results. However, a distinction must be drawn between probable and known valid biomarkers as currently most pharmacogenomic measurements are not considered valid biomarkers.

Regarding national differences, the consensus among respondents was that there are no major differences between the EU, the USA and Japan in the case of PGx regulations. Minor differences were perceived in the following areas:

- Lack of harmonisation and regulatory and legislative differences between the EU Member States make it more difficult to do clinical work in the EU. This is logistical work and the number of centres that can be handled in a multi-centre study is limited by this fact.
- In comparison to the USA the more pro-active behaviour of the FDA in developing the regulatory framework was seen as an advantage for US companies.
- The comparison of the FDA and the EMEA could be summed up as the FDA actively engaging with industry to work out regulatory procedures and the EMEA being less active. The following points were made:
  - The FDA is "more interested in science".
  - The FDA is "actively looking at issues and staying abreast". – The EMEA is "only watching".
  - "The EMEA knows what it is doing but is not getting involved."

Consequently, according to the experts, the most important task for the future is action by the EMEA to ensure clear guidance and handling of PGx. The EMEA's briefing meetings were welcomed by the representatives of industry, but do not go far enough. Obtaining final clarity on what is needed from the regulatory agency for PGx is still the challenge facing industry with regard to regulatory approval. Some respondents feared that the EU would not be ready for PGx submissions because of the apparent inactivity of the EMEA.

On international harmonisation, experts had mixed feelings. According to the interviews, on the one hand, national differences exist (e.g. problems in Germany with federal ethics committees or in France with high data protection requirements) but on the other harmonisation should not be over-emphasised. Some experts stated that if harmonisation was carried out too early it tended to solidify legislation. This could lead to less flexibility, whereas flexibility is an advantage in the early stages of introduction of a new technology.

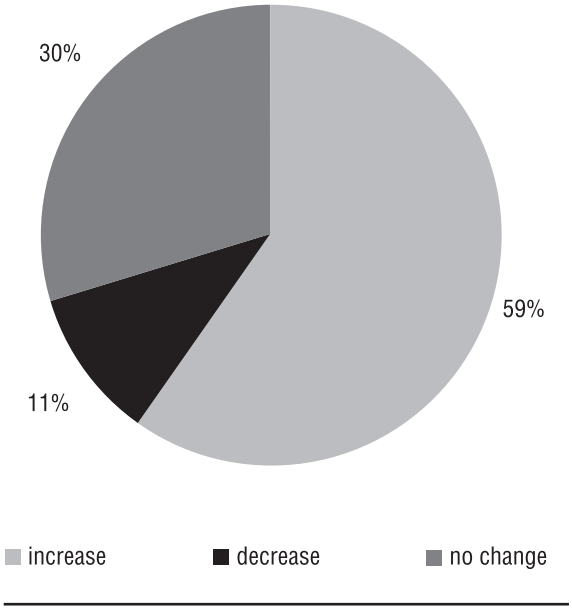
The European In-Vitro Diagnostic Directive (Directive 98/79/EC) and the measures transposing it into national law were not an issue for the companies interviewed during this study. The Directive regulates the production, distribution and operation of medical devices with the aim of ensuring their safety, appropriateness and operating efficiency for patients and users and has no negative impact on PGx activities.

2.4.3 Research funding

2.4.3.1 Public sector

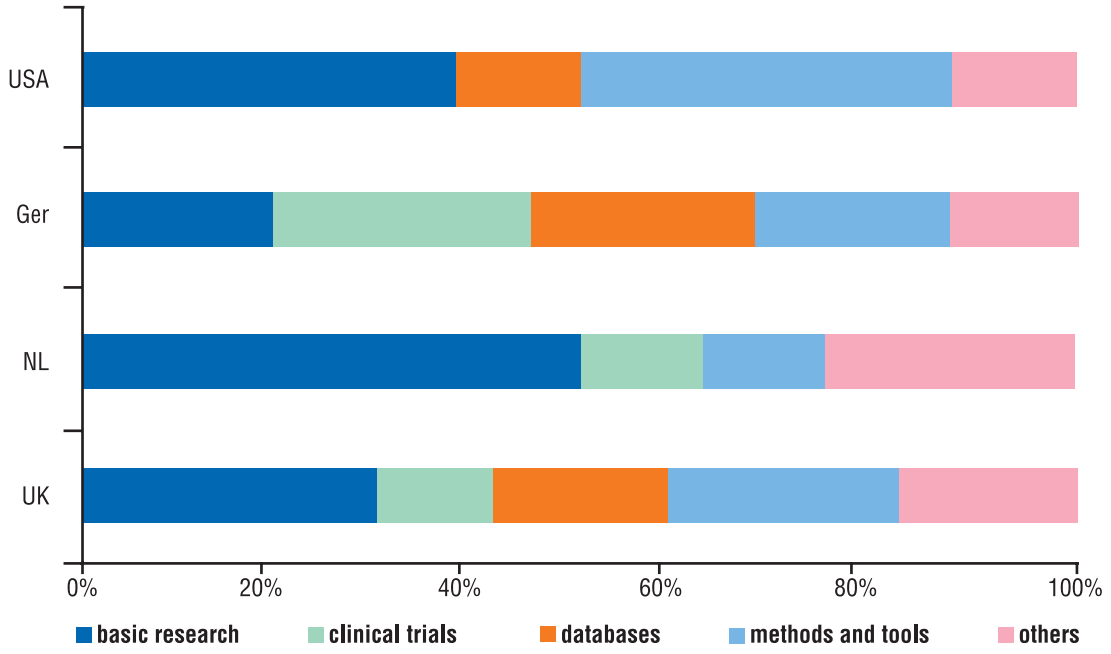
PGx is a very dynamic field. During the last five years the total budget increased in nearly 59% of all research groups answering and another 30% maintained the same budget over that period. Only 11% reported a cut in their budget (see Figure 2-15). The average budget of academic groups participating in the online survey was roughly €300 000. As most research groups are part of university or public research organisations which cover the costs for most personnel this budget is mostly for materials, costs of clinical studies, etc. A comparison between research budgets in Europe and the USA revealed that US research groups have on average twice the research budget of European groups. Several respondents attributed this difference to the massive activities started by the NIH Pharmacogenetics Research Network (PGRN) (cf. Chapter 4.3). These activities were described as a means to catch up with the pioneering work carried out in Europe between 1986 and 1998 by the COST B1 programme ("European collaboration on the study of inter-individual differences in drug disposition and action"). However, in the opinion of most of the European researchers interviewed, in the mean time the USA has achieved its goal and overtaken European research in terms of scientific output (see ranking of research institutions).

Figure 2-15: Development of total budget of research groups over the last 5 years



Most research groups (95%) stated that it is still difficult to raise adequate funding for all research activities. Money gaps affect both basic and applied research almost equally (see Table 2-6). However, the proportion varies from country to country. Whereas financing of basic research seems to be a bigger problem in the Netherlands, in Germany clinical trials are under-represented in

Figure 2-16: Proportion of money gap by country and field of activity



the financing plans (see Figure 2-16). The national differences are due to the heavy dependence of research groups on core funding from the government.

As shown below, a high proportion of public research is financed by core funding from the government (see Figure 2-17). Industrial contracts and funds from foundations play a minor role and contribute to the group's budget only on the basis of individual projects (e. g. data collection, development of a test) (see Figure 2-18 and Figure 2-19). EU funding for PGx was used by only six - less than 10% - of the research groups questioned.

Table 2-6: Money gaps in research financing

Money gap	Number of responses
Basic research	29
Development of tools and methods	28
Clinical trials	22
Development of databases	19
Others	12

Figure 2-17: Public funds for individual research projects from national sources (as % of total budget in 2003)

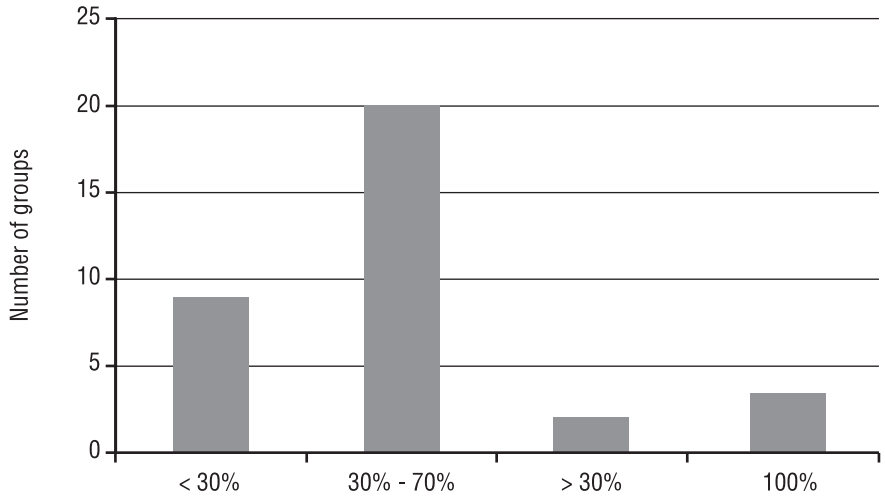
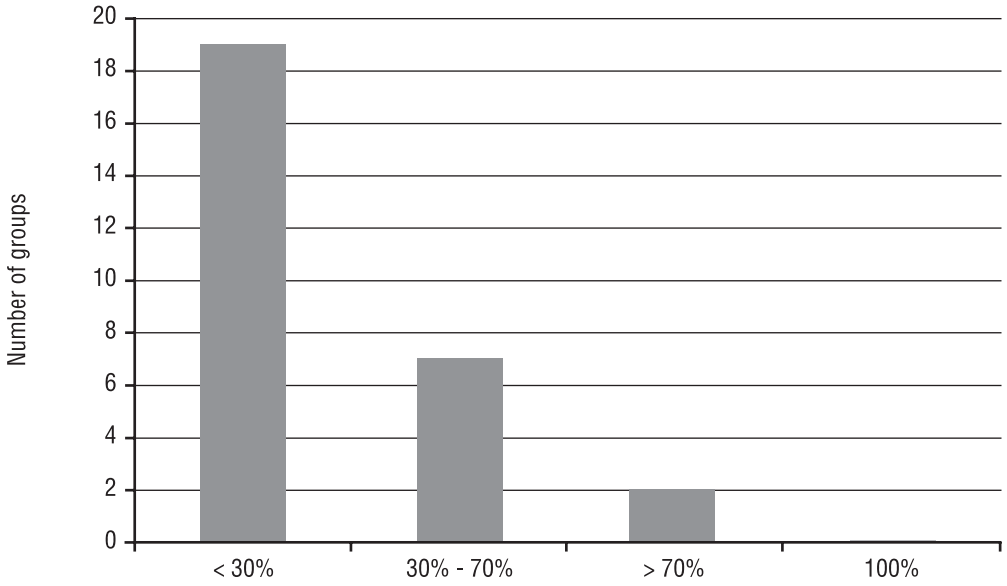


Figure 2-18:Funds from industrial contracts (as % of total budget in 2003)



Although FP6 offered the opportunity for PGx funding, researchers complained about the heavy administrative burden and unclear requirements (see Figure 2-20). A strong network covering the whole area of PGx was not accepted for funding from FP6 and indication-based projects were favoured according to one respondent. This discouraged many European initiatives.

2.4.3.2 Private sector

Most companies self-financed their PGx research. Some are carrying out or have carried out publicly funded research projects (mainly in collaboration with academia). Most companies interviewed, however, stated that the administrative barriers are too high to save any money. However, networking through publicly funded projects is important for companies, and most were very positive about their interest in becoming involved in the networks created by FP projects. Some companies even have staff monitoring these activities. Even companies which replied that they were involved in an FP activity were not aware of whether they were receiving any funding, indicating that the funding aspect played a minor

Figure 2-19:Funds from foundations and charities (as % of total budget in 2003)

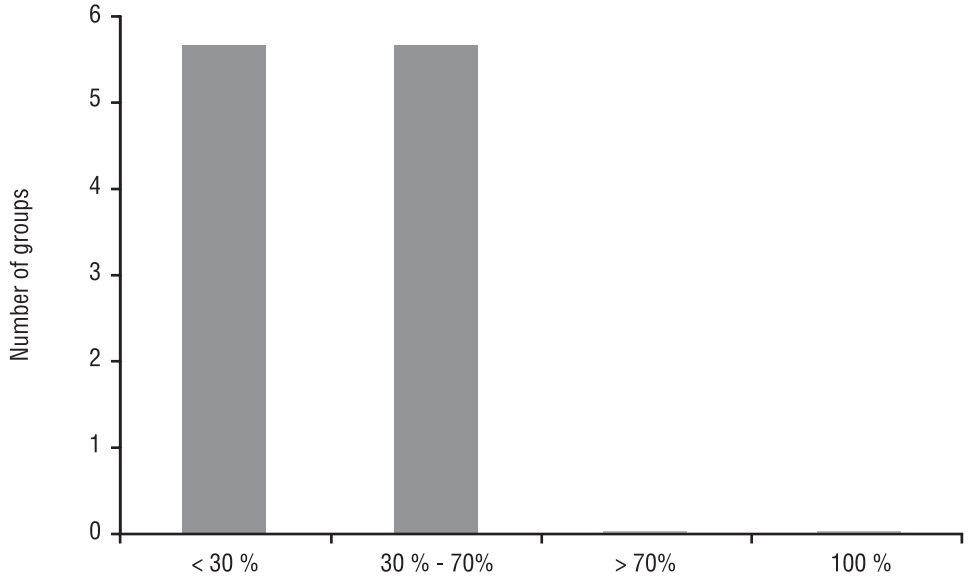
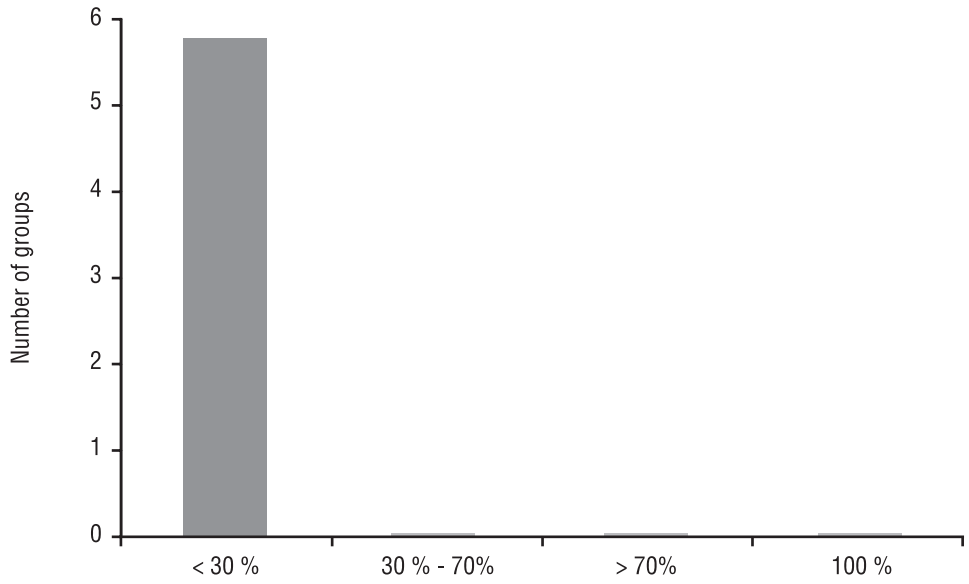


Figure 2-20: Funds for projects from the EU Framework Programme (as % of total budget in 2003)



role in their involvement. The general perception of public funds can be seen from the following comments:

- "It (funding from the Framework Programme) looks very difficult to get your hands on."
- With regard to NIH involvement …"the money saved is not worth the pain in the neck."
- "…too much time required (in applying) for too little money."

Many companies pointed to the need to revise the public funding programmes to make it easier for companies to become involved in useful collaboration. At present programmes did not always fit the industry's needs.

2.4.3.3 Value added by PGx

Expert opinion in both the public and private sectors was at one on the time scale for any significant impact of PGx. It has already had some impact on drug discovery and development. Most experts estimated that it would take 20 to 25 years for PGx to have a significant impact on public health. They assumed that within 3 to 5 years PGx tests could be standard practice for some indications, i.e. an average person will be screened for some genetic conditions and some drugs with compulsory PGx testing for dose adjustment will be approved.

Regarding savings, experts calculated that the pharmacotherapy of 10 to 30% of all drugs in use could be improved by PGx. According to some estimates this would lead to a cost saving due to fewer ADRs and better efficacy in the range of US$ 177 billion per annum in the USA [15]. Drug development costs could be reduced by 50% [16]. However, for over half of all drugs it might not be possible to relate patient genetics to drug response because the genetic determinants are too complex to define. Moreover, a myriad of non-genetic factors affect drug response (such as diet, previous disease history, liver and kidney disorders, environmental emissions, physical conditions, physical activity, smoking, alcohol consumption, etc.). This will be a demanding task requiring continuous research in the field of pharmacogenomics with an as yet unclear time-frame.

3. Socio-economic impact: clinical implementation

Although 50 years of public PGx research and more than a decade of strategic activities by the private sector have considerably promoted this field, as described in the previous chapter of this report, PGx is still not broadly applied in the clinic. One of the reasons for this could be the technical, regulatory, knowledge and socio-economic barriers. In order to gain insight into the practical aspects of implementation and associated socio-economic issues of pharmacogenetics and pharmacogenomics (PGx) in Europe, two cases where pharmacogenetic testing is already employed in clinical practice were evaluated to reveal possible economic and social barriers: HER2 (efficacy of trastuzumab) and TPMT testing (safety of thiopurine drugs). These two case studies cover both key applications of pharmacogenetics, i.e. improvement of drug efficacy and reduction of adverse drug effects, and could therefore provide insight into the current social and economic issues. Four countries were selected for these case studies: Germany, Ireland, the Netherlands and the United Kingdom.

The qualitative evaluation of the case studies includes the manner in which the tests were introduced on the market in each country surveyed, which is also related to introduction of the drugs for which these tests are employed. The evaluation describes how TPMT and HER2 testing came into being, the development and approval process and the role of specific players such as clinicians, industry and patients' organisations in each of the four EU countries. It covers the social and economic issues related to each of the two tests, such as economic aspects (including impact of the tests on the drug market), the reimbursement situation (who pays for the expensive test and drugs), and social and ethical issues mostly dealing with patients' views and attitudes towards the tests. Informed consent and perception aspects are also analysed.

A quantitative assessment was carried out of the cost-benefit ratio in the four EU countries for use of TPMT in acute lymphoblastic leukaemia (ALL) and HER2 in breast cancer.

3.1 Background

3.1.1 Case 1: Human epidermal growth factor receptor (HER2)

The cloned human epidermal growth factor receptor 2 (HER2), associated with a form of metastatic breast cancer, emerged as a potential monoclonal-antibody therapy target in 1985. As a result the humanised IgG1 monoclonal antibody "trastuzumab" with high affinity and specificity for HER2 was developed, and clinical trials were started in 1992. In 1998 the drug was approved in the USA by the FDA as "Herceptin". This drug was given fast-track approval status for two reasons: it demonstrated efficacy in patients previously resistant to more conventional treatments and a diagnostic test was able to identify patients who could be expected to benefit from Herceptin. Herceptin was approved in Europe in 2000 by the EMEA's centralised procedure (CP).

The HercepTest is the first example of a pharmacogenomic test that is marketed along with a drug. Some have argued about the genetic nature of this test. The 2000 OECD definition[17] says: "*Genetic testing is testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects.*" The HercepTest detects an overexpression of receptors, caused by the presence of more than two HER2-gene copies. Although the presence

17 www.oecd.org/dataoecd/46/37/1895646.pdf.

of these extra gene copies is related to somatic changes that take place during tumour growth and does not represent a germline genetic variation, this is still a case of measurement of the product from these extra gene copies. In this sense, the HercepTest could and will be considered as a pharmacogenomic test.

Herceptin is approved for the treatment of breast cancer patients and should be used only in patients whose tumours have HER2 overexpression, determined by immunohistochemistry (IHC), fluorescence in-situ hybridisation (FISH) or other methods.

Recent comparison of FISH and IHC shows that FISH appears to be superior at providing prognostic information with respect to the detection of higher risk breast cancers. Unfortunately, it is expensive and requires additional equipment and training to that routinely found in most laboratories. For this reason, various parties recommend that only IHC results showing little overexpression of HER2 should be retested with FISH to prevent false-negative outcomes which would deny the drug to patients who might benefit from it.

3.1.2 Case 2: Thiopurine methyltransferase activity (TPMT)

In 1953 the "wonder drug" 6-mercaptopurine (6MP) was put on the market in the USA. Later it was launched in Europe, under the brand name "Purinethol". Expectations were high in the medical world, and many children were cured of leukaemia. About 20 years ago, however, researchers discovered that the drug could be extremely toxic for 0.3% of the patients. The same scenario was repeated with azothioprine, launched on the market in Europe and the USA in 1968 as "Imuran", where toxicity and fatal sepsis were reported in transplant patients.

Polymorphisms in the thiopurine methyltransferase (TPMT) gene are responsible for the large inter-individual differences observed in TPMT activity. Patients with two defective copies of the TPMT gene are at a higher risk of thiopurine-induced toxicity. Later, evidence was also found that patients with very high TPMT activity might display lower therapeutic efficacy when treated with standard doses of thiopurine drugs. In the 1990s a DNA test to predict toxicity became available in the USA.

Because overdosing of thiopurine drugs could result in haematological toxicity or fatal sepsis, it is vital to know a patient's TPMT level before starting the therapy. The phenotypic TPMT assay is carried out using red blood cells as the source of the enzyme. The blood sample is combined with the substrate 6-thioguanine and the quantity of a reaction product, 6-methylthioguanine, is then measured by HPLC, by a radiochemical assay or by other chemical methods. The amount of the reaction product indicates the level of TPMT activity.

One major drawback with phenotyping is that thiopurine drugs can stimulate an increase in the patient's TPMT levels which could mask an inherited deficiency in TPMT levels. A further complication with phenotypic TPMT measurements is that the anaemia associated with ALL produces a downward shift in blood TPMT activity. Although patients with extremely low TPMT activity can be determined by the phenotypic assay, intermediate TPMT levels in ALL sufferers are best determined by phenotypic testing once the patients are on maintenance therapy. This does not apply to patients taking azathioprine, or adults taking 6MP as an immunosuppressive. Basal activity can be accurately predicted before drug treatment starts, as TPMT activity does not change during low dose immunosuppressive therapy (lab 2).

Another drawback is that unreported blood transfusions can create a misleading impression of the patient's metabolic TPMT activity, as in this case the phenotypic TPMT assay would be influenced by the TMPT activity of the blood donor erythrocytes [17]. Patients with low TPMT activity might therefore be missed if the phenotypic assay is carried out within a few days of a blood transfusion.

Genotype assays for TPMT do not suffer from these drawbacks. The basic molecular genetic testing methodology developed in the mid-1990s

for detection of mutations associated with TPMT deficiency utilises PCR combined with restriction enzyme digests to detect manually the presence or absence of a specific DNA sequence at a known locus [18]. Already several US companies (especially Prometheus)[18] have developed a series of tests for TPMT activity (genotype, enzyme activity and metabolite screening) which they offer as a service, although the relative strengths and weaknesses of the methods they employ have not been investigated in this study.

3.2 Clinical practice

3.2.1 HER2 test and clinical practice

The e-mail survey on HER2 produced a response rate of 27% (Germany 24%, UK 31%, Netherlands 33% and Ireland 7%). Amongst the respondents, 8% give treatment with trastuzumab without any testing, and another 8% use the test but do not test all patients who receive the treatment. The actual level of committed, consistent use (implementation) of HER2 testing is 84%. Further interviews with clinical staff gave a more detailed view of the situation in each country.

In Germany immunohistochemical HER2 testing is now an integral part of routine laboratory testing of tumour tissue in most hospitals. However, the actual number of cases in which Herceptin could be prescribed is at a much lower level than reported in studies and is equivalent to a maximum of 20% of breast cancer patients. It seems that not all women diagnosed as having HER2-positive breast tumours automatically receive trastuzumab. The main hindrance is the perceived cost-benefit ratio of Herceptin. Herceptin is seen as a much too expensive treatment bearing in mind that it provides no cure, but can only extend the length of a patient's life for a few more months. The method of application is also criticised. Herceptin is currently applied via infusions once a week which impairs the patient's quality of life and is accompanied by other side-effects, some of them severe. Herceptin was not regularly prescribed in the hospital surveyed in Germany, due to high costs.

The test can also serve merely as a means to forecast the probable development of the cancer. HER2/neu receptor status is now routinely measured in every mammary carcinoma in the majority of German hospitals, at least by immunohistochemical staining.

In Ireland HER2 is now used as a standard test in all hospitals and clinics involved in breast cancer therapy, and is conducted on virtually all patients presenting with breast cancer. Irish hospitals have historically had their own in-house analytical laboratories and no moves are being made to centralise testing. Cancer therapy is, however, centralised within certain hospitals and therefore specialised testing such as HER2 will be of relevance only to laboratories within these specific hospitals. Consequently, laboratories deal with only small numbers of HER2 test samples. However, these hospitals may sub-contract certain low-volume tests to a particular hospital, as they have done with HER2, where the Dublin hospitals have centralised testing in Tallaght General Hospital. In the whole country approximately 2000 HER2 tests are conducted per annum. These are histochemical tests, and are routinely requested by oncologists.[19] The major Irish centres also use the FISH test which they seem to prefer as being less subjective than the HER2 test. One respondent added that the FISH test was preferred because it allows assessment of the effects of the treatment on gene expression. Active research has also been conducted to develop easier sampling methods, using fine-needle aspirates, for tumour samples prior to using the FISH test [19].

In the Netherlands each year about 11 000 women are diagnosed with breast cancer, 20% of whom overexpress the HER2 protein. In 2004 the Dutch Institute for Healthcare Improvement

18 See http://www.prometheuslabs.com/212a.asp?nav=products accessed on 23.1.2005.
19 Interview with clinical biochemist consultant.

(CBO) and the National Breast Cancer Platform (NABON) published "screening and diagnostics" guidelines for the treatment of breast cancer which stated that the test should be used for each breast cancer patient because it forms – together with other inputs – a basis for an informed decision on the therapy to be used. In January 2005 the Dutch Society of Oncologists accepted these guidelines. Following this decision the tests are now included in hospital budgets. In the hospitals in which clinicians were interviewed, the test is now conducted as part of the standard procedure. It is one of a set of tests (including analysis of oestrogen and progesterone levels) depending on the characteristics of the tumour. Market research by Roche showed that in 2003 one third of the 110 hospitals used the HER2 test as standard procedure. Another one third performed the test only on special request by the oncologist, and the last one third did not use the test at all. According to the company, Herceptin is prescribed mostly in the western part of the Netherlands and in very few cases in the rest of the country.

The industry has played an important role in introduction of the HER2 test and Herceptin. DakoCytomation markets its test by informing and training pathologists. Experts from the company assist pathologists with conducting the test and help them to interpret the results and values. Test samples are sent to pathologists so that they can practise interpretation. Alongside this, the company assists with "diagnostics over the phone; remote diagnostics over the internet; on-site fault finding; preventive maintenance inspections; software and hardware upgrades; and providing warranty and service contracts" (http://www.dakocytomation.com). For the FISH test DakoCytomation has developed extensive e-learning training on the internet, and a newsletter is sent to professionals to keep them informed about new knowledge and prescriptions. Besides this, the representative interviewed explained that the company organises meetings (with support from Roche) to make pathologists aware of the necessity to conduct the test in the right way.

Roche promotes use of the HER2 test because, according to the company representative interviewed, it *"prefers to sell the right medicine to the right person instead of selling the medicine to people who do not benefit from it"*. In the Netherlands, Roche did not want to subsidise the test and/or the medicines, according to the respondent from DakoCytomation, because *"it did not work that well in the UK either"*. DakoCytomation argues that its cooperation with Roche on the Dutch market is important. Both companies have organised a meeting to inform Dutch pathologists about HercepTest™ and the related quality requirements.

It can be concluded that clinicians/ oncologists – particularly at specialised cancer hospitals – together with the industry have played a leading role in introduction and implementation of HER2 and Herceptin in the Netherlands. The influence of breast cancer patients on this process has been relatively limited. Once both test and drug became known (the internet played an important role), patients began to ask for it. They have pushed clinicians to do the test and, in case of HER2 overexpression, use Herceptin and have mobilised the Breast Cancer Society.

In the UK about a year before Herceptin was due to be launched, Roche carried out market research that showed comparatively low levels of HER2 testing in the NHS. In Spain, France, Italy and Germany about 40% of metastatic breast cancer patients were tested for HER2 overexpression, while in the UK only about 6% were tested.[20] This is supported by talks with histopathologists, one of whom suggested that the UK "started with a very low base….There were very few centres that were routinely doing HER2 testing in breast cancer at that time….This contrasted with the [United] States where I think it was close to 90 percent".[21]

20 Roche interview, 25.10.2002.
21 Interview CR18, 4.6.2003.

The reasons for this limited uptake of HER2 testing in the UK are varied, but include the cost of the test and the subsequent effect on how clinicians view its clinical value. Roche considers that this resistance was based on financial concerns, namely the UK's status as "one of the worst countries in Europe for putting funding behind cancer drugs".[22] In addition there is a degree of scepticism about the value of such tests within the UK oncological community. The histopathologist quoted above summarised the situation as follows: "In this country there has been, and I think there persists, a thought that you don't do testing unless there is a real reason to do the testing".[23] The result is that clinicians doubt whether HER2 testing is particularly useful in terms of prognosis: "It's largely irrelevant. In a way, in this context, it's more how the lymph nodes are positive, how aggressive is the tumour, what grade, what size is the tumour".[24]

This is clearly at odds with the position of the American Society of Clinical Oncology (ASCO) which has recommended that HER2 "overexpression should be evaluated on every primary breast cancer" [20] and with the views of Roche which supports the idea that HER2-positive tumours are resistant to some forms of chemotherapy and HER2 status is of value as a prognostic indicator.[25]

The solution to this reluctance to testing was two-pronged. First, Roche aimed to overcome clinicians' cost-driven scepticism about HER2 testing and, second, it decided to make Herceptin available to clinicians even though it had not been approved for use on the NHS. To get clinicians into the "habit" of HER2 testing Roche decided to fund all HER2 testing in the UK for a period running up to and past the introduction of Herceptin into the NHS, a solution that was described as unique to the UK and the Irish Republic.

From October 1999 to the end of March 2003 Roche allowed any clinician in the country to send samples for testing, free of charge. The company had planned to stop testing at the end of March 2002, but the decision on use of Herceptin on the NHS was delayed, and Roche continued funding the reference centres for another year. One factor behind this decision to carry on funding testing was the continued resistance: by March 2002 "the testing situation had gone up to about 27% in the UK, in terms of metastatic breast cancer patients being HER2 tested, but the rest of Europe was ahead of 70-80%, so we were still quite far behind, so we felt that we should support it for a little longer".[26] Since 1 April 2003 the references centres are no longer funded by Roche, but the company has maintained a degree of control over HER2 testing in the UK by working with one of the centres to provide HER2 testing, on a commercial basis, to smaller laboratories that might not feel confident about their expertise.

As mentioned earlier, Roche set out to ensure not just that clinicians were used to HER2 testing, but also that they were prescribing Herceptin, even before the drug was approved for NHS use by NICE. Roche wanted to get the drug "out there", to get clinicians using Herceptin, so that if and when NICE approved it, there would already be a degree of clinical experience. Roche's solution was to initiate an expanded access programme, an idea which is largely taken from AIDS activists in the late 1980s, who pressured companies into allowing them to take drugs before they had received FDA approval. This programme started in January 2000, making Herceptin available to 168 patients free of charge and allowing it to be purchased by certain hospitals under special licence between December 1999 and September 2000.[27] Roche is still supplying Herceptin to at least one recent respondents' patients who do not

22 Roche interview, 25.10.2002.
23 Note that this scepticism is not just related to HER2 testing but should be seen as a broader community response. For example, similar resistance could be found to oestrogen receptor status testing, which identifies patients eligible to receive Tamoxifen.
24 Interview CR2, 31.1.2002.
25 Roche interview, 25.10.2002.
26 Roche interview, 25.10.2002.
27 Roche interview, 25.10.2002; Interview CR4, 1.3.2002.

fit the strict NICE criteria.[28] Oncologists obviously appreciated this free provision, although they accept that there are powerful commercial interests driving it: it was often referred to as a "glorified marketing scheme".

HER2 testing was introduced at different times in different hospitals. Some places in the UK, usually laboratories with a strong research interest, developed HER2 testing in the late 1990s, while other hospitals, perhaps just down the road, did not start testing until Herceptin became available.[29] Because of the Roche testing centres, there was no necessity to develop HER2 testing capacity as soon as Herceptin was licensed for use: when hospitals undertake their own testing, they use one or other of the approved tests (either the DAKO HercepTest or the trial antibody CB11).[30] Introduction of Herceptin, prior to NICE approval, varied across the country; around half of all health authorities agreed to fund some Herceptin. Sometimes patients had to go to the press and campaign to get this funding agreed.[31]

3.2.2 TPMT test and clinical practice

The results from the e-mail survey showed a very low level of consistent use of the test, at only 12% of all cases with no significant differences between the four countries. Out of all respondents who treat with thiopurine drugs, 53% give treatment without prior use of a pharmacogenetic test and a further 35% use the test, but do not test all patients who receive the treatment.

In Germany treatment of ALL accounts for only 10% of the TPMT tests conducted. According to the interviews, TPMT testing is often only applied after the event to trace back the cause of the adverse reaction.

In Ireland, in contrast to Germany, all children presenting with leukaemia are routinely tested for TPMT status prior to treatment. This is mainly for clinical reasons, as it is useful both to identify TPMT-deficient patients and also to individualise the dosage. Clinicians added that medicine is now practised in a highly litigious environment. Failure to test could result in malpractice claims in the event of side-effects, and this is another motivation.

Irish hospitals have historically each had their own in-house analytical laboratories and there is currently no move to centralise such testing. Cancer therapy is, however, centralised within certain hospitals and therefore specialised testing such as TPMT will be of relevance only to laboratories within these specific hospitals.

In the Netherlands TPMT testing in children with ALL was introduced after extensive basic research by the Department of Paediatric Oncology in Nijmegen since 1980. Financial support for the research was provided by the Dutch Cancer Society. From 1997 until 2000 TPMT levels of all children in the Netherlands with ALL were measured several times during their treatment with 6MP. However, now that these research projects have finished, standard testing is no longer conducted.

To date, testing on TPMT deficiency has been centralised. The laboratory in Nijmegen is the only laboratory in the Netherlands that offers testing on TPMT deficiency, either by an enzyme test, which involves direct (phenotypic) measurement of enzymatic activity, or, more recently, also by DNA testing. The latter takes the form of a home-made validated genetic test which screens for mutant alleles associated with TPMT deficiency. The heads of the laboratories consider that DNA testing has advantages over enzyme testing, especially because blood transfusions during therapy can increase TPMT activity in TPMT-deficient or in heterozygous patients because of a mixture with the higher-activity donor erythrocytes.

28 Interview with senior oncologist, 20.1.2005.
29 Interview C2, 16.12.2002.
30 Interview with oncologist, 4.2.2005; Interview, 3.2.2005.
31 Interview with oncologist, 3.2.2005.

Currently all children with ALL are treated according to the standard (DCOG-ALL-10) protocol. Along with the treatment, weekly or two-weekly measurements are taken of leukocyte and trombocyte status. Based on this, the dose of 6MP will be monitored and reduced or increased if necessary. This protocol does not include standard testing for TPMT deficiency before the start of treatment. However, it is recommended to test for TPMT deficiency in cases of severe or persistent haemotoxicity. The DCOG-ALL-10 protocol advises physicians to request the laboratory in Nijmegen to conduct TPMT testing.

In the UK at present TPMT testing for ALL is funded by the Leukaemia Research Fund as part of the UKALL 2003 clinical trial. ALL is the most common childhood cancer in the UK, but the majority of patients survive the disease.[32] Every ALL patient is offered the opportunity to join the trial and the vast majority clearly do so as between 350 and 400 children affected by ALL join the trial each year. A total of 1 900 patients were enrolled in UKALL 1997 and around 2 300 are expected to join UKALL 2003 (lab 2).[33] UKALL national-scale clinical trials for leukaemia are currently ongoing in the UK. At present the laboratory associated with the UKALL 2003 trial remains the only laboratory offering a TPMT testing service for ALL patients in the UK (lab 1, lab 2, lab 3).

3.3 Barriers to clinical uptake

Clinical implementation of the two tests studied has been shown to be incomplete and the e-mail survey and interviews tried to analyse the main reasons for this. Table 3-1 shows possible

Table 3-1: Hospitals perceiving a barrier to clinical implementation (number and %)

Possible barrier	For HER2	For TPMT
Costs		
UK	9 (60%)	0 (0%)
D	19 (54%)	5 (55%)
NL	9 (47%)	n.d. (*)
Storage of the sample		
UK	3 (20%)	0 (0%)
D	8 (23%)	2 (22%)
NL	1 (5%)	n.d.
Sending of the sample		
UK	9 (60%)	1 (17%)
D	6 (17%)	2 (22%)
NL	2 (11%)	n.d.
Communication with laboratory		
UK	8 (53%)	1 (17%)
D	11 (31%)	3 (33%)
NL	3 (16%)	n.d.
Testing capacity of the laboratory		
UK	7 (47%)	0 (0%)
D	7 (20%)	2 (22%)
NL	3 (16%)	n.d.
Reluctance of employees		
UK	2 (13%)	1 (17%)
D	3 (9%)	1 (11%)
NL	2 (11 %)	n.d.
Asking for informed consent		
UK	1 (7%)	0 (0%)
D	2 (6%)	2 (22%)
NL	0 (0%)	n.d.

(*) not determined, due to low representation in the sample.

32 According to the patient information leaflet for the ALL 2003 trial available at: http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc, accessed on 1.4.2005.

33 See also the patient information leaflet for the ALL 2003 trial available at: http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc, accessed on 1.4.2005.

barriers to HER2 and TPMT testing and the percentage of hospitals which perceived them as such, though the response in the case of TPMT was too low to draw conclusions. It shows how the technical infrastructure (communication, sending of samples to laboratories and storage of samples) is often problematic. This is most problematic in the UK. Costs were also reported as being a barrier to testing.

3.3.1 Infrastructure barriers

In delivery of pharmacogenetic testing to the patient, communication with the laboratory performing the test procedures is important for transferring information [21]. Other possible barriers to consider are the sending and storage of the sample, i.e. the "physical infrastructure" aspects. As shown in Table 3-1, problems with laboratory communication vary from one country to another. The UK respondents using HER2 tests have significantly more problems with laboratory communication, while Dutch hospitals perceived the fewest problems with HER2 testing.

3.3.2 Unclear reimbursement practices

The e-mail survey on clinical implementation confirmed the obvious premise that reimbursement of the costs is extremely important. As an example, one laboratory in the Netherlands openly pointed to the fact that it does not carry out TPMT testing routinely because reimbursement has not yet been arranged. Similarly in the UK no NHS reimbursement is available and testing is currently paid for from research funding. The answers from the respondents were inconsistent, with disagreement over whether or not reimbursement was available. The highest consensus was amongst the HER2 respondents from the UK, the majority of whom (73% for public and 80% for private insurance) answered that the test is fully reimbursed. Furthermore 80% of these UK respondents agreed that HER2 testing is a requirement for reimbursement of trastuzumab. In Germany and the Netherlands the consensus about full reimbursement and a testing requirement (for public and private insurance) was less clear on between 50 and 60%. For TPMT the number of respondents was too low to draw conclusions.

The interviews revealed that respondents were not at all familiar with the current procedures for reimbursement of the tests and yielded a large amount of differing information.

3.3.2.1 HER2 testing and reimbursement practices

In Germany the FISH technique for HER2 testing is still funded by Roche even after official approval of the test in November 2004. This procedure has to be seen against the background of the reimbursement system. It is up to the Federal Joint Committee (G-BA) and the German Common Board of Physicians and Insurance Companies ("Bundesausschuss der Ärzte und Krankenkassen") to decide upon reimbursement of a pharmaceutical or medical device respectively. Common practice to steer or influence this process is to disseminate the innovation in advance amongst doctors and to gain patients' trust. Combined with the competitive situation among insurance companies, this is expected to produce a positive outcome to the decision-making process.

In Ireland since its introduction HercepTest is supplied free of charge to user laboratories as part of Roche's programme to promote use of Herceptin. The company provides significant support to user laboratory staff and to physicians using Herceptin, in the form of information, training, an on-going help-line and web-based information.

In the Netherlands, as the HER2 test and Herceptin are used only when the patient is in hospital, the costs of tests and drugs are paid through the hospital's budget. This is the virtual budget agreed upon each year by the national government, hospitals and health insurance companies. This budget sets the maximum costs for patient care that can be charged by the hospital and will be reimbursed. This limited budget implies that not all tests and drugs that are needed to give optimum patient care can be used.

The average costs of treatment with Herceptin are €20 000 per patient. About five HER2-positive patients per hospital per year are treated with the drug. As a result, if a patient with breast cancer is the sixth or seventh with a positive HER2 test result at the hospital that year, there is a very realistic chance that she/he will not be treated with Herceptin for lack of funding. Therefore patients – not only breast cancer patients but also patients that have to be treated with other expensive drugs – "shop around" in other hospitals (that have not yet exceeded their budget) and even go abroad in order to get their treatment, according to the Breast Cancer Society, despite the CBO guidelines encouraging all hospitals to use the HER2 test and Herceptin. According to the Breast Cancer Society, hospitals still often do not inform their patients as they should. *"Ask, ask and ask again"* is what it tells its members.

Alongside this, according to DakoCytomation, the situation would also improve if there were a reimbursement scheme specifically for pharmacogenetic tests. Diagnosis and therapy should be regarded as an inseparable combination, argue both Roche and the Breast Cancer Society.

At the same time as Roche was persuading UK oncologists to accept HER2 testing and Herceptin, the drug was being reviewed by NICE, the National Institute for Clinical Excellence. NICE's role is to determine whether particular treatments are clinically and cost effective and whether they should be available on the NHS. NICE's appraisal of Herceptin began in September 2000, lasted until March 2002, and was one of its more controversial decisions [5]. As usual during a NICE appraisal, a great deal of lobbying and publicity took place, with Roche, breast cancer charities and clinicians all attempting to persuade the Institute to give a positive response.[34]

It is important to note that NICE did not regard the Herceptin decision as special by virtue of the drug's pharmacogenetic nature: "The Institute makes its decision not on, is it pharmacogenetic?..[but]…on what the evidence is that's available".[35] "Of course, it is quite possible that an organisation like NICE would be open to an approach which selected smaller numbers of patients for particular treatments. […] we've been able to target the drug at areas where it may be more clinically and cost effective. Arguably, if this pharmacogenetic issue is true, then yes, you could say the targeting has been done for you. However, of course, if they are incredibly expensive, then the overall analysis would still mean they might be clinically effective but not cost effective in that debate".[36] Since then, all health authorities have been required to provide Herceptin to women who meet NICE's criteria.

A survey carried out by the UK Breast Cancer Coalition (an alliance of breast cancer charities) in September 2002 suggested that funding for Herceptin had come on-line, but that there was confusion over where exactly responsibility for monitoring provision lay.[37] More recently, concerns have been voiced about the provision of HER2 testing by the charity Breast Cancer Care, whose Chief Executive said that "there is evidence that not all eligible women are having their HER2 status tested. NICE guidance on Herceptin was issued two years ago, and it is imperative that this guidance is fully implemented so that all eligible women with advanced breast cancer receive the best patient care and treatment possible. We believe it is essential that high-quality testing facilities for HER2 are in place throughout the UK".[38] This is supported by one respondent who suggested that by restricting provision of HER2 testing, health authorities were keeping Herceptin prescription costs down. Since they are obliged to

34 Roche interview, 25.10.2002; Charity interview, 19.6.2003; Interview with charity 2, 12.6.2003.
35 Interview with NICE representative, 7.7.2003.
36 Interview with NICE representative, 7.7.2003.
37 Breast Cancer Coalition (2003). Press release: Are NICE-approved treatments reaching cancer patients?
38 Breast Cancer Care (2004). Statement on HER2 testing and Herceptin.

give Herceptin to HER2 overexpressing women, by limiting the amount of testing carried out they limit the number of eligible Herceptin recipients.[39] This is a serious problem which might have legal consequences in future.

For private health provision, the situation seems different. In terms of assessing the suitability of particular treatments, these organisations tend to accept a broadly defined "clinical consensus" as supporting provision. In the case of Herceptin, the NICE approval served as a very public indicator of such consensus, and private health insurers seem happy to pay for this treatment. The problem they find is that because some clinicians are reluctant to send NHS patients for HER2 testing (perhaps because of economic worries), this reluctance spills over into *private* patients, even though reimbursement would not be a problem. It is as if the HER2 "habit" that Roche tried so hard to instil in the UK oncology community has been undermined by continuing funding concerns.

3.3.2.2 TPMT and reimbursement practices

For TPMT testing in Germany, given that reimbursement is not only determined by the separation of the market into public and private insurance schemes but also depends on different bodies of rules and regulations in different inpatient and outpatient settings, products and tests are being reimbursed separately. Specifically both PCR (genotype) and RBC (phenotype) TPMT tests are being reimbursed. Yet physicians claimed that, especially in the case of RBC which is far more widespread, the sum refunded did not cover the actual costs, potentially creating a hurdle for wider application.

Regarding future PGx applications, it is always up to the Federal Joint Committee (G-BA) ("Gemeinsamer Bundesausschuß") and the Common Board of Physicians and Insurance Companies to decide on the reimbursement situation. Representatives of private insurance companies claimed that they usually follow the decisions taken by the G-BA.

As there are also misunderstandings about "will the treatment given be reimbursed" further communication between the attending physician and the controlling department should be advocated.

In Ireland all treatments using TPMT-relevant diagnostics and therapies are fully reimbursable in both systems of medical cover.

At present TPMT testing for ALL in the UK is funded by the Leukaemia Research Fund as part of the UKALL 2003 clinical trial. This funding is expected to continue until 2007, but cease thereafter as after 10 years of support the LRF feels the test should be adopted by the NHS and is hopeful that it will be (charity 1). Currently the NHS does not pay for any TPMT testing associated with ALL although TPMT testing is reimbursed with NHS funds at other UK laboratories serving physicians who prescribe Azathioprine.

The largest private health insurer and provident association in the UK is BUPA. The position set out here does not necessarily reflect the view of BUPA, but was provided by a BUPA employee. BUPA receives little demand from customers for claims concerning severe illness in children. This is mainly due to the small number of private hospitals due to stringent child safety regulations and strong NHS provision in the UK. BUPA has therefore not needed to consider reimbursement for TPMT testing related to ALL specifically, and generally seems unaware of any demand for reimbursement of TPMT testing.

Overall BUPA considers that pharmacogenetic testing has valuable contributions to make to medicine, but so far these have been slower to emerge than had been expected. The lack of progress in this field to date was felt to reflect more than just the usual slow advance of medicine. It was pointed out that genetics is a field that has been particularly susceptible to hype given its political cachet.

39 Interview with oncologist, 3.2.2005.

3.3.3 *Financial barriers*

Cost is a common barrier to application of novel medical technologies and in this survey costs were indeed seen as a problem for both HER2 and TPMT tests (see Table 3-1).

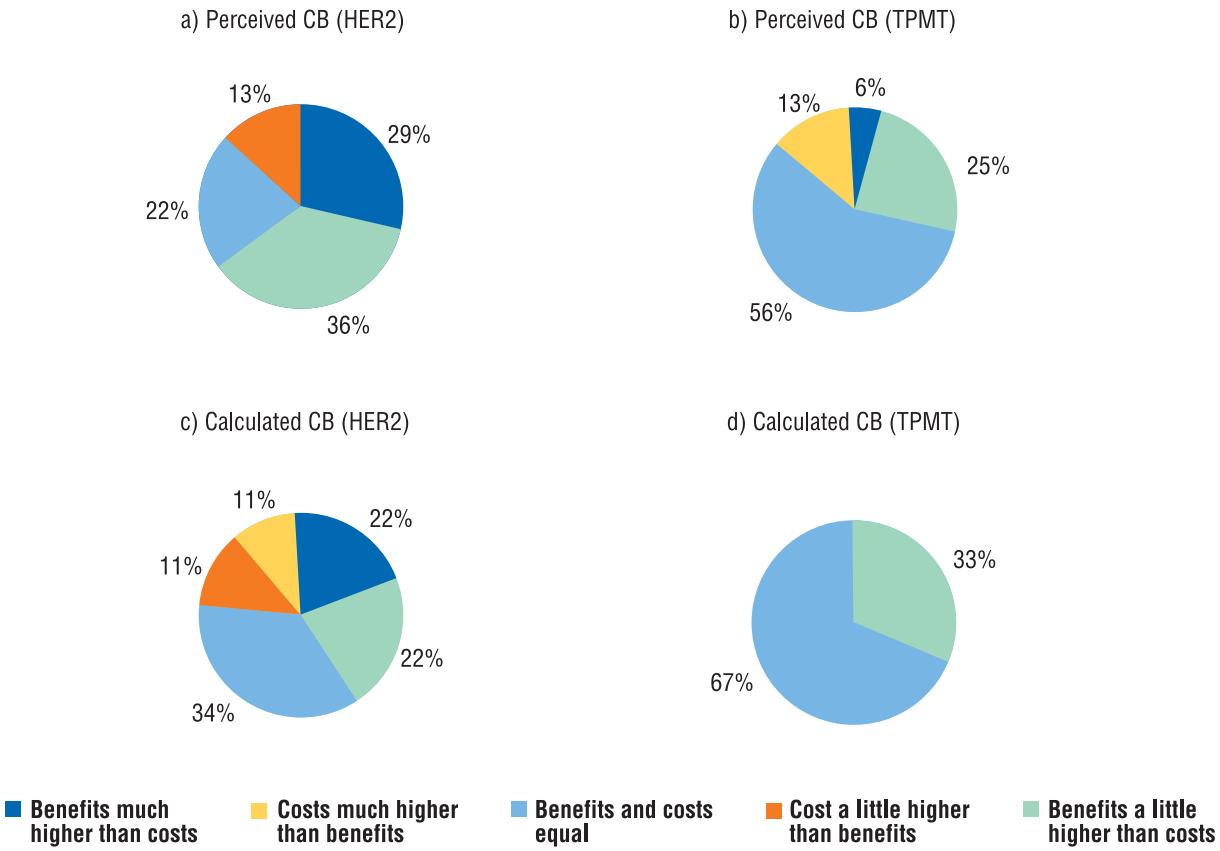
A physician could perceive a test as cost-beneficial, but it is also important to see whether calculations have actually been made. For this reason, both perceived and calculated cost/benefit ratios were included in the survey. Respondents were not asked about the methodology used to make their calculations. The survey shows that respondents perceive HER2 testing as having more benefits than costs (see Figure 3-1). The UK has the most positive perception of HER2 testing and the Netherlands the least positive. Out of all respondents, 13% for HER2 and 20% for TPMT had made calculations about the cost-benefit ratio. The outcome led to a cost-benefit ratio slightly more negative than the perceived ratio (see Figure 3-1). HER2 test-users' perception of the cost/benefits ratio is clearly more positive than for TPMT users, a significant proportion of whom even consider the costs of TPMT testing much higher than the benefits.

As the lower half of the figure shows, the calculated CB ratios vary widely, which stresses the need for standardised calculation methods. Larger hospitals and departments with a higher percentage of recently educated doctors make such calculations more often.

3.3.4 *Knowledge barriers*

An appropriate level of education is necessary if adequate use is to be made of any new medical technology. Genetics is no exception. Whether or not MDs have difficulties interpreting the results

Figure 3-1: Perceived vs. calculated cost-benefit ratio (CB) of HER 2 and TPMT testing



of the tests can be a good indicator of a further need for specific education [22]. In each country, between 16 and 20% of respondents consider interpretation of HER2 results "difficult" and under 11% find TPMT results difficult.

Knowledge about the existence of the tests is not always sufficient either. Roche mounted an intensive campaign to promote the use of the HER2 test with trastuzumab treatment. No such campaign has ever been launched for TPMT. As one of the Dutch respondents said: "I am not sure what to do with TPMT testing. We receive thiopurines from our pharmacy, and if any testing would be necessary we assume that our pharmacy will tell us". This example highlights the lack of knowledge among physicians, and the need to educate pharmacists about PGx as well [23].

Several reasons were mentioned to explain why TPMT testing is not very widely used among physicians despite the apparent cost/benefit ratio. In the literature, a presumed deficit in physicians' knowledge of genetic issues is often discussed [12] (p.109). The apprehension that doctors are not knowledgeable enough to interpret the test results properly seems right. One German respondent stated that human genetics did not became a compulsory subject during medical studies until 2000. Taking into account that the average age of German doctors is 50.2 years,[40] many of them were not properly educated in this field. There is evidence that pharmacogenetics and pharmacogenomics will need to be made a more integral part of the curriculum in German universities so that the next generation of young doctors has better genetic knowledge. In general, opinions on the level of such knowledge which has to be acquired in order to apply PGx knowledge adequately diverge among the persons interviewed. The majority believe that very broad skills to explain the issue to the patient and to advise the patient adequately are enough. Only in certain very vague cases should a human geneticist be contacted. It was up to the laboratory to give adequate instructions to the doctors. The problems that arise from this need will be discussed thoroughly later.

One German respondent had already tried to push this knowledge by offering courses on the subject, but the response rate had been very low. She put that unwillingness to participate down to an information overload - it was hard to distinguish between relevant and useful information and less useful information amidst the mass of news inundating the physician - together with a lack of flexibility (a strong belief in tried and tested methods that have long been in use combined with feeling uncomfortable about adjusting to changes).

A lack of trust also prevails about the meaning of genetic tests as their results are only one among many different variables leading to a different reaction. Despite the proof that other external factors rarely have any influence in the case of TPMT, this view predominates.

Another laboratory stated that one reason for the current hesitation is that scientists and companies hyped up the subject very early when there was no proof of high correlation and no application on the market. Now it was seen as hard to revive this enthusiasm.

In the Netherlands various reasons were mentioned during the interviews to explain the lack of testing in the standard treatment for children with ALL. The most important reason mentioned by physicians for not introducing TPMT testing is the lack of perceived benefit. "There is no-one who really feels such a benefit to introduce TPMT testing for all children with ALL". They see no perceived benefit in several respects. The first is that there will always be toxicity during treatment of these patients.

One important reason mentioned by a laboratory specialist (from the biochemical and molecular laboratory) is the lack of knowledge among physicians about TPMT deficiency itself

40 Ärztekammer (2005).

and the availability of the TPMT test. Often no adequate data exist to guide doctors about the practical conclusions to draw from the relevant results. There is no standard way of informing or educating physicians. Until now, the heads of the biochemical and molecular laboratories have been informing physicians by organising lectures and giving presentations during (international) conferences but there is no structured dissemination of knowledge about the test.

In the UK the perceived technical complexity of assays has made it difficult to establish wider testing in the UK (lab 3). However, the disadvantages seem mainly to indicate the need to address organisational issues within the therapeutic regime or quality control issues in the laboratory rather than being insurmountable technical obstacles.

Dissemination of knowledge could also be a problem but attempts are being made to develop and implement electronic prescribing and advisory systems in clinics, which can contribute to improving the situation. One laboratory interviewed, together with a university hospital, is currently attempting to merge two existing databases into a combined database that contains very detailed information for doctors who prescribe a drug.

TPMT testing for ALL in the UK has been described as on the threshold of moving from a research test to a service test because, although widely used, at present it is not funded by the NHS (consultant haematologist 1). However, cost is not seen as too much of an obstacle by users as the test is not particularly expensive and individual oncology departments see only 10 to 40 cases of ALL per year. This cost is seen as relatively small given that the NHS already spends many thousands of pounds per year treating each ALL patient (consultant haematologist 2), although laboratory reports suggest that this might not be the view of other medical specialities where the costs and benefits of the test are not so favourably aligned (lab 1).

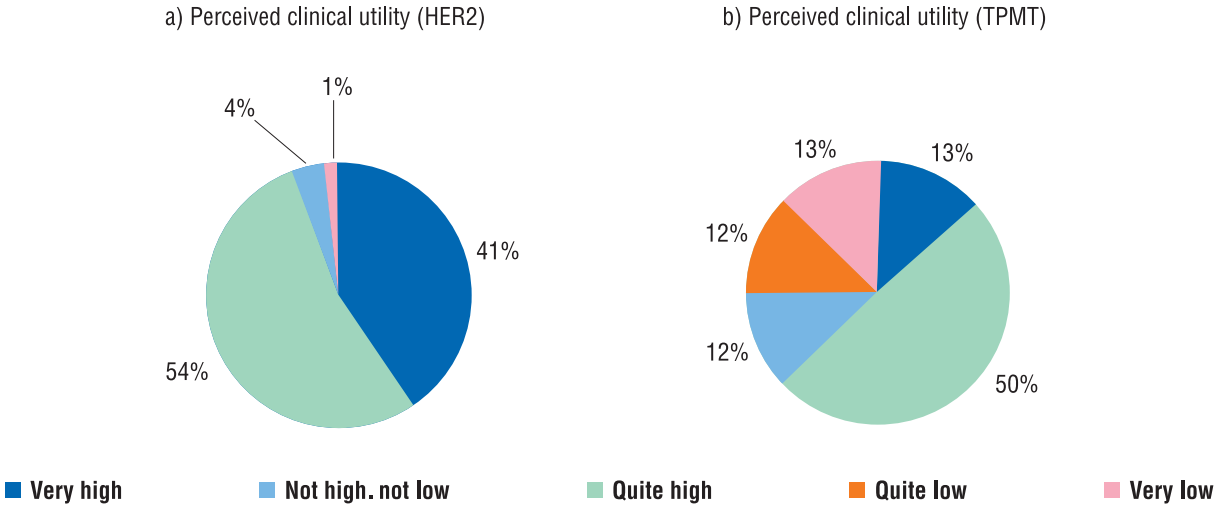
The test is relatively easily integrated into existing practice, as mentioned previously. However, while some clinicians seemed to think that take-up of the test was very high in the ALL trial, other clinicians and the laboratory indicated that a significant proportion of oncology departments did not fully comply with the guidelines for sending samples before prescribing TPMT, despite the test being freely available and part of the required trial protocol. This is not peculiar to the ALL trial. Looking at TPMT testing in the UK as a whole, it seems that, regrettably, some physicians are not sure to be diligent until after close experience of adverse reactions (labs 1 to 3).

Education of the users, be they physicians or other staff members, is therefore another potential hurdle. The trend in the UK is towards increasing division of labour, with nurses and pharmacists being given roles as supplementary prescribers. These professionals also need to be educated in use of PGx tests. It is questionable whether they would be willing or able to take on these additional responsibilities (pharmacist 2). On the other hand having a dedicated member of junior staff whose duty is to collect such samples is reportedly helpful, as occurs in one institution where a research nurse was employed (consultant haematologist 3). This is useful because the low volume of ALL patients seen by most departments, means that many staff will be unfamiliar with the full details of the trial protocol (consultant haematologist 3).

The nature of ALL treatment means that often patients will be given blood transfusions, perhaps before they join the trial, and in these circumstances accurate TPMT testing using the phenotypic test can be difficult, as mentioned earlier. However, the genotypic test is available in the trial laboratory so that these patients can be given this test if more suitable. But unless staff understand the importance of informing the relevant person about the transfusion the laboratory would not know that it might be supplying an invalid result (consultant haematologist 3).

Apart from the clinical issues, technically the phenotypic test is cumbersome and difficult to establish for new users. Where new laboratories are required to offer a service in the UK or in other

Figure 3-2: The perceived clinical utility of TPMT and HER2 testing



countries, the difficulties of the assay may hamper dissemination. In particular, the assays currently used are "home brews" and depend on substrates which, in some cases, have been problematic to obtain (lab 3). Only in one case is the assay used CE marked.

The therapeutic benefit, i.e. clinical utility, is probably one of the most important keys to the success of a medical innovation. As can be seen in Figure 3-1, the majority of respondents perceive the clinical utility of HER2 testing as quite high or very high. For TPMT testing, the clinical utility is perceived as quite high by the majority of respondents (50%), but also as quite or very low by a certain proportion (12% and 13%). There seems to be broader consensus on the clinical utility of HER2 testing compared with TPMT testing. One obvious reason for this could be the availability of the red blood cell count (RBC) alternative to TPMT testing. Several respondents explained that they do not use the genetic test, because research is in progress to determine whether genotypic or phenotypic methodologies should be used and which is the more suitable. As a consequence, the red blood cells are often monitored any way, which lowers the relevance of the genetic test.

3.3.5 Societal barriers

Public acceptance is not the strongest determinant of effective clinical implementation, but lack of it could certainly doom any new healthcare technology to failure. Although use of genetic tests in medicine is broadly accepted by the public in Europe,[41] the study tried to investigate whether there is public/patient resistance to pharmacogenetic testing.

According to the respondents, patients are sometimes worried about the test results but this could be because of the implications for their prognosis and treatment and they hardly ever refuse a test.

Due to the nature of genetic tests it is extremely important to gain proper informed consent. However, the results of the survey indicate that

41 Gaskell G, Allum N, Stares S. Europeans and biotechnology in 2002. Eurobarometer 58 [online] 2002 [cited 30 March 2005]. Available from: URL: http://europa.eu.int/comm/public_opinion/archives/ebs/ebs_177_en.pdf.

in practice physicians using pharmacogenetics always request informed consent, and very few departments reported informed consent as a significant burden (see Table 3-1).

Most of the physicians believed that patients' organisations have a positive attitude towards HER2 testing. In the case of TPMT, most physicians think that patients' organisations have a neutral attitude. This information raises no specific social issues, but interviews with patients are needed to gain more insight into the situation.

3.3.5.1 HER2

There was a clear consensus on the potential benefits that patients can derive from pharmacogenetic applications. It seems quite acceptable to sift out in advance patients who will not benefit as every medication is accompanied by side-effects. Screening frees patients from additional stress and prevents false expectations, according to some respondents.

There is concern that patients who show only a marginal chance that the drug might help - talking about mere probabilities - will not have access to the drug at all. This is a critical issue that is not yet solved.

Given that the tests determine a somatic genotype, retrieving additional information was not perceived as a future problem. However, knowledge on the probable development of the disease can be seen as supplementary information. As HER2 overexpression is linked with a bad prognosis of the progression of the disease, this information can also weigh heavily on the patient. Therefore, no special informed consent or education process has been designed. HER2 testing is part of a whole range of tests being conducted on breast cancer patients.

IRELAND

The respondents stated that there are currently no societal issues related to the use of HER2 tests in Ireland. The Irish Cancer Society, which is a major independent source of information on cancer, gives information on this form of therapy without referring to any significant difference from other types of treatment. The staff of the Irish Cancer Society helpline were also surveyed on possible resistance by patients to the genetic nature of the HER2 test or to other aspects of Herceptin use. In their experience, no patient had ever differentiated between the HER2 test and any of the other tests used in cancer diagnosis or therapy monitoring. They also reported, however, that Herceptin was not widely known among patients. This contrasts with experience in Germany, as described in the Fraunhofer report.

NETHERLANDS

For HER2 testing it is not common to request informed consent in the hospitals surveyed. The hospitals ask for a standard statement in which the patient agrees with the hospital's policy to use human material for different purposes.

The clinicians interviewed mentioned that the patient does not receive technical information about all the ins and outs of the test, because it is seen as standard procedure. Therefore, according to a clinician from the NKI/AVL, it is "*nonsense*" to ask for informed consent, simply because the test is part of a certain treatment of certain characteristics of tumours. "*If the patient disagrees, they are free to choose another hospital of their liking*". As soon as it is shown that there is a genetic component in the breast cancer, the patient is forwarded to professional genetic counselling.

Another clinician argued that patients are informed that the HER2 test is about the presence of specific proteins in the cells. Presence of the protein means a bad prognosis and other treatment schemes. After testing, patients are informed whether the results are positive or negative. If the result is negative, the test will not be further discussed.

UK

In the UK patients' organisations pushed very hard for the introduction of Herceptin and are continuing to lobby for access to the drug on the NHS. In the case of Herceptin, there is no counter-argument to HER2 testing. HER2 overexpression is a requirement both for the pharmaceutical licence and for NICE's approval and, beyond that, clinicians would be unlikely to be willing to prescribe a potentially dangerous product without checking to see whether a patient might benefit. Patients' groups do not seem to have a specific position on informed consent to HER2 testing (see below) other than a general preference for respecting patients' autonomy.

On the whole, patients in the UK are not told in advance that their tumour tissue is going to be tested for HER2 status.

When patients come to the clinic consent is obtained for a biopsy to sample the tumour and patients may well be told that a number of tests will be run on the tumour tissue, but HER2 testing is rarely singled out for specific mention and the exact details of HER2 and Herceptin are rarely discussed with patients before the results become available. Therefore the respondents could give no examples where a patient had refused an HER2 test, since they are rarely, if ever, informed of the test.

Oncologists do not ask for consent for HER2 testing for a number of reasons. First, HER2 testing is not the only test run on the tumour sample and pressure of time means that it would be difficult to discuss the full range of tests run on a sample with each patient. Although Herceptin is viewed as a useful treatment, oncologists are unsure as to its status as pharmacogenetics, especially since the kind of genetic variation involved is not inherited and therefore does not raise many of the issues that "normal" genetic testing does.[42] In many ways HER2 and Herceptin have much in common with ER status testing for decisions on prescribing Tamoxifen, a practice that has been in use for 15 years.

After a positive result, when the test and its treatment implications are explained to them, patients vary in their ability to get to grips with the mechanics of the test. Some, but obviously not all, patients have difficulty understanding what the test implies. In fact, some patients actually ask for Herceptin; they are aware of the drug and want to be tested for HER2 status.[43]

The clearest issue mentioned by respondents was the need for adequate funding of Herceptin and HER2 testing. Despite the NICE requirement that all health authorities provide Herceptin to patients with metastatic breast cancers which overexpress HER2, provision is still patchy.

"The affected individual is willing to try everything that provides the slightest chance of help," was the most common statement among respondents. As both indications are life-threatening, this knowledge represses all other feelings of doubt.

Regarding the potential benefits that patients can derive from pharmacogenetic applications, there was a clear consensus among the parties questioned. The safety of medicines, i.e. avoidance of adverse reactions, was most frequently mentioned. A potentially higher rate of patient compliance due to more "individualised" therapy options was also reported. One common counter-argument against a potential rise in compliance was that patients discontinue taking medicines because of possible side-effects that cannot be reduced by better targeting the medication (such as loss of hair, virility problems, etc.).

Various ethical or societal problems that could occur in the course of introducing pharmacogenetic methods were reported. Among them were data protection fears regarding misuse of the data by insurance companies and employers, the storing of samples within clinical trials and anonymisation of the data gathered. Concerning

42 Interview with oncologist, 3.2.2005.
43 Interview with oncologist, 3.2.2005.

these issues, very controversial opinions were recorded.

Physicians and some laboratory staff as well as representatives of companies play down the issue and compare PGx data to familiar genetic traits which have not proved to be a concern such as "blood group determination" and "colourblindness". Others, including patient groups and authorities, are more cautious.

Opinions also diverge on the derivation of supplementary information regarding predisposition to other diseases. Two reasons were stated that suggest there is no potential problem:

First, only one correlation has been found up to now (arylamine N-acetytransferase 1 (NAT1) and a possible predisposition to urinary bladder cancer) despite further progress in research and, second, these correlations are characterised by a multifactoriality – even in the case of NAT1 - that the real probability of developing the disease in question is very low. Still, the counter-argument is that the field is very immature and further research might reveal other critical correlations. One difficult question raised was how to react if a correlation is detected at a later stage - tell the patient or not? These issues have to be clarified now and regulatory efforts are on the way.

3.3.5.2 TPMT

TPMT was seen as the best example in the field of PGx, as it screens for a genetic polymorphism which would disturb nobody under normal circumstances. "A homo- or heterozygous patient can live to 150 years old without any disturbances because of that." Or in the words of another physician: "On a disease predisposition, e.g. Alzheimer, one has to test specifically, such information does not simply occur."

In addition, in the case of TPMT, a very small variety of products is influenced very strongly by these mutations, whereas in other cases, a very wide range of medicines is influenced relatively slightly, as in the case of CYP2D6. Therefore, TPMT is really worth testing without having to fear any impact in other areas.

The biggest concern on the part of patients is a lack of time allocated by physicians to counsel the patient. They feared that this problem could grow even more acute in view of the importance of the decision to take. More and more patients start seeking information on their own as they do not feel adequately informed by the doctors. There was no agreement on whether – at least in certain cases - a human geneticist should be contacted.

Considering the poor state of knowledge among physicians themselves regarding these correlations, it is no wonder that patients are not at all familiar with the existing possibilities and risks. This is a topic at medical congresses and in professional journals that do not reach the general public.

As stated above, no company has a commercial interest in TPMT testing. Therefore, in contrast to HER2 testing, no action is being taken to educate patients directly. Because of existing information asymmetries - a common problem in evaluating a physician's performance - patients are dependent on the doctor's competence and willingness to keep up with these new currents.

No social or ethical issues arose during the discussions with clinicians or others about TPMT testing. Given the nature of the disease, there is no resistance to the testing protocol and questions about the nature or purpose of testing are rare. Often the TPMT test is only phenotypic and there is therefore no requirement for specific patient consent to taking the sample. If further genetic tests are introduced, this could change.

The major legal issue in this area appears to be clinicians' motivation to avoid malpractice actions by ensuring that all possible pre-screening that could avoid adverse reactions is conducted. TPMT is clearly a case where it is prudent to ensure that all patients are pre-screened.

In the development of the UK ALL clinical trial protocol no special consideration was given to the wider implications of revealing the genetic status of individuals to the families of TPMT-deficient patients. No objections were raised to this stance when the research project came before the

childhood leukaemia working party (composed mainly of haematologists and oncologists) which oversees all leukaemia trials in the UK (consultant haematologists 1 and 2). The LRF also found no cause for concern with this situation (charity 1).

Although obtaining informed consent prior to diagnostic testing is considered an important principle (lab 1), in practice many patients involved in the UK ALL clinical trials are not informed of the nature of the TPMT test prior to the procedure and the information given to patients makes no specific mention of the pharmacogenetic test for TPMT.[44] However, patients or their parents are asked to sign a consent form for the trial as a whole, including the research projects attached, of which TPMT testing is one (consultant haematologists 1 and 2).

The low priority given to informing patients of the test reflects the view of clinicians and laboratory staff using TPMT testing within the context of ALL that the genetic basis of poor or deficient thiopurine drug metabolism is not of particular concern to the families of patients who are coping with a life-threatening disease, as the test is seen as part of the solution to the problem of drug toxicity or ineffectiveness (consultant haematologists 1 and 2, lab 2). At some sites it seems that in general patients are not told about the test unless they are found to be TPMT-deficient, but at other sites the family is told (consultant haematologist 3). Either way it seems that when this situation is discussed the test is seen as a good thing because it is helping to resolve the issue of why a potentially life-saving drug treatment has become problematic. In practice, in the context of the treatment (which places a huge burden on the family) the genetic implications of the test "play an extremely minor role" (consultant haematologist 1). It is conceded that in any other circumstances a test revealing a genetic characteristic might raise concern, but in this particular context the combination of the life-threatening disease and the mass of information relayed to families is suggested as a reason why further discussion of TPMT testing would not be considered a priority by patients or practitioners (consultant haematologist 1, pharmacist 2).

There is uncertainty about the natural role of the TPMT enzyme (which, of course, did not evolve to metabolise thiopurine drugs), so the full implications of being deficient are not known (lab 1). However, as far as is known, being TPMT-deficient has no implications unless the individual takes thiopurine drugs.

However, the possibility of a family being faced with a recurrence of disease in another family member with deficient TPMT activity is considered remote, but not entirely unfeasible. Nonetheless laboratory staff do not consider that the genetic basis of TPMT deficiency should be a significant concern to family members beyond the patient (lab 1, lab 2, lab 3). Overall, there seems to be clinical scepticism about genetic exceptionalism with regard to TPMT testing. This was summed up by consultant haematologist 2: *"People worry about all genetic testing but quite frankly we need to know that result… I don't think that having a low TPMT level will affect anyone's insurability or affect their mortgage or anything like that".*

This view reflects the broader situation in the UK where private health insurance is purchased by only a minority due to the broad coverage of the NHS. A moratorium agreed between the Association of British Insurers and the government on the use of genetic testing in insurance in almost all circumstances has been in place for several years and is likely to remain until at least 2011.[45]

As patients have little opportunity to discuss the test it is not clear to what extent they may understand or object to it on the basis of its possible ethical implications. One clinician's response was that any objections were likely to be very rare: *"You are not doing [the test] out of*

44 See http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed on 1.3.2005.
45 http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4106051&chk=2CNwmM accessed on 1.4.2005.

interest. There have been deaths in patients who have been [TPMT] deficient. It is a significant finding" (consultant haematologist 2).

3.3.6 Legal barriers

There is no regulatory framework imposing consistent testing. One legal aspect often mentioned in literature is prevention of liability issues by means of pharmacogenetic testing [24]. Fear of liability is likely to increase uptake of pharmacogenetic tests as a technology that helps to protect doctors against litigation [25]. One respondent from Germany had a clear opinion on the liability issue: "Most clinicians giving azathioprine are getting more and more aware of the fact that if they give thiopurines to a TPMT non-metaboliser and that patient develops a severe adverse reaction, the clinician will be held responsible."

In this survey, 38% of the HER2 respondents thought that pharmacogenetic testing prevents liability issues and 11% thought that this is not the case. A higher percentage (50%) of TPMT respondents believed that pharmacogenetic testing prevents liability issues while 12% believed that this is not the case. The remaining respondents expressed no specific opinion on this.

Another legal factor that might support introduction of pharmacogenetic testing would be regulatory requirement of the test.

If a physician did not use the TPMT test when it was available and the patient subsequently suffered an adverse drug reaction, the issue of culpability was considered to be valid because *"in oncology if you don't follow [the protocol] the patient dies"* (consultant haematologist 1). The parent information sheet for the clinical trial also clearly states that negligence could be grounds for legal action.[46] However, there was no mention of this having arisen in the context of the ALL clinical trials.

3.4 Cost-effectiveness of pharmacogenomics in clinical practice

Although an increasing number of applications of pharmacogenomics are described in the literature, so far there has been little exploration of the economic implications. This could be partly due to the fact that pharmacogenomics is in its infancy. However, clarifying the economic implications of pharmacogenomic treatment strategies could facilitate their implementation, which heightens the need for economic evaluations of pharmacogenomic treatment strategies. Other topics, such as ethical and legal aspects, have to be studied as well, before a well-considered decision about implementation can be made.

Analysing the cost-effectiveness of a pharmacogenomic strategy involves comparison of the cost and effects of the pharmacogenomic strategy compared to current medical practice. Factors that play an important role in this comparison are the genotype of interest, the genomic test, the disease state and the treatment. In general a pharmacogenomic strategy is likely to be cost-effective when (i) the polymorphism under consideration is prevalent in the population and has a high degree of penetrance; (ii) the available genetic test is highly sensitive and specific; (iii) the disease state involves significant morbidity or mortality if left untreated; and (iv) the treatment involves significant outcomes and/or costs on which genotype-individualised therapy can have an impact [26].

Pharmacogenomic strategies for improved clinical treatment regimes can be divided into two main categories: 1) pharmacogenomic strategies for increasing treatment efficacy and 2) pharmacogenomic strategies for improving drug safety, i.e. decreasing drug toxicity and adverse drug reactions (ADRs). HER2 and TPMT testing include both these categories. The main objective of performing these analyses was to evaluate their

46 See http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed on 1.3.2005.

impact on clinical implementation and also to review the data available for this type of studies and the degree to which economic considerations influence clinical uptake. The importance of this type of analysis is clear in a society with heavy health expenditure, as discussed in the reflection paper published by DG SANCO in July 2004 on the New EU Health Strategy.[47] This is considered an area where the EU can foster synergies between Member States, and the Commission has already committed itself to help mobilise Community instruments for health.[48]

For both cases - HER2-testing and TPMT-testing - models were developed for comparison of the costs and effects of the pharmacogenomic treatment strategy with current medical practice, and the model parameters were identified. The model parameters concern economic, genetic and clinical data.

Subsequently information on model parameters was collected from literature and experts in the countries participating (Germany, the United Kingdom, Ireland and the Netherlands). The analyses were performed from the societal perspective, the preferred perspective for economic evaluations. This means that all costs and effects are included regardless of who incurs the costs and who benefits [27].

Costs are in euros at 2004 rates. If the costs were from other years, the effect of price inflation was removed by using the harmonised annual average price indices of the different countries to inflate the data to 2004 values.

3.4.1 Review of cost-effectiveness analysis in pharmacogenomics

As mentioned earlier, cost-effectiveness analysis is a widely used tool to assess the value of healthcare interventions. Several published articles apply this kind of analysis to the field of pharmacogenomics [28];[29];[26]. However, it is rarely used in pharmacogenomics. Phillips & Van Bebber [1] performed a systematic review of cost-effectiveness analyses of pharmacogenomic interventions and identified only 11 studies that met their inclusion criteria up to and including July 2004. This means that both the costs and effects of a programme were compared with at least one alternative, this comparison was presented as a ratio, and sufficient details were provided for a minimal analysis as described by Gold et al.[27].

In the meantime another cost-effectiveness analysis has been published by Winter et al. [30]. The most commonly examined disease was deep vein thrombosis (n=4) followed by

Table 3-2: Characteristics of cost-effectiveness analyses of pharmacogenomic interventions

Article	Mutation name	Drug name	Primary outcome measure	Primary cost-effectiveness result
Auerbach et al. (2004)	Factor V Leiden plus other	Warfarin	Cost/QALY gained	Favourable
Creinin et al. (1999)	Factor V Leiden	Oral contraceptive pill	Other	Not favourable
Eckman et al. (2002)	Factor V Leiden	Warfarin	Cost/QALY gained	Equivocal
Elkin et al. (2004)	HER2/neu	Trastuzumab	Cost/QALY gained	Equivocal
Marchetti et al. (2000)	Factor V Leiden	Warfarin	Cost/QALY gained	Favourable
Marchetti et al. (2001)	Factor V Leiden plus other	Warfarin	Cost/QALY gained	Favourable
Marra et al. (2002)	Thiopurine methyltransferase	Aziothiopurine	Other	Favourable
Oh et al. (2003)	Thiopurine methyltransferase	Aziothiopurine	Other	Favourable
Weinstein et al. (2001)	HIV variants	Highly active antiretroviral treatment	Cost/QALY gained	Favourable
Winter et al. (2004)	Thiopurine methyltransferase	Aziothiopurine	Other	Favourable
Wong et al. (1998)	Hepatitis C virus genotypes	IFN-α-2b	Cost/QALY gained	Not favourable
Younossi et al (1999)	Hepatitis C virus genotypes	IFN-α-2b plus ribavirin	Cost/QALY gained	Favourable

47 http://europa.eu.int/comm/health/ph_overview/strategy/reflection_process_en.htm.
48 "Building our common future: Policy challenges and budgetary means of the enlarged Union 2007-2013", COM(2004) 101 final of 10.2.2004.

cancer (n=3) and viral infections (n=3). The most frequently examined mutation factor was factor V Leiden (n=5). The majority of the studies reported a favourable cost-effectiveness ratio for the pharmacogenomic-based strategy (n=7), two reported that the pharmacogenomic intervention was not cost-effective and two were equivocal. Details of the studies are presented in Table 3-2.

Phillips & Van Bebber concluded in their 2004 systematic review that there have been few evaluations of the economic costs and benefits of pharmacogenomic interventions and that they have covered a limited number of conditions.

3.4.2 TPMT

Model parameters were identified and searched for in the literature and from experts in each country. In general, little information on the parameters for the TPMT model was specifically available for children with ALL. Therefore, estimates from pharmacoeconomic studies on other thiopurine drugs are frequently used [31], [32], [30].

TPMT activity in the general population

The distribution of TPMT activity in the population depends on ethnicity. This study used the distribution found in Caucasians. The majority of individuals (88.7%) have high TPMT activity, corresponding to the homozygous wild-type genotype. Approximately 10% of the population are heterozygotes at the TPMT gene locus and have intermediate TPMT activity. Homozygotes with two TPMT mutant alleles have deficient TPMT activity and account for 0.3% of the population [33].

Adverse events

Myelosuppression was reported in 1 to 11% of patients by one of the experts. Sanderson et al. (2004) reported a frequency of 1.4 to 5%. Winter et al. [30] assumed the frequency of leucopenia in adults with inflammatory bowel disease treated with thiopurine drugs to be 3.2%, based on the results of seven studies. For patients with rheumatological conditions treated with azathioprine, Marra et al. [31] assumed the probability of haematological cytopenia to be 0.09%. Other adverse events include allergic reactions (2.3%), nausea, vomiting, lack of appetite, diarrhoea (1.4-5%), pancreatitis (1.4-5%) and infections (7%). These adverse advents were not included in the cost analysis, as their costs are assumed to be comparatively minor.

However, pre-evaluation of TPMT activity or gene status will not eliminate all cases of myelosuppression. Marra et al. [31] assumed that 50% of the cases of haematological toxicity could be eliminated by screening for TPMT and dosage reduction. Sanderson et al. [34] report that 29% of the adverse reactions are the result of overdosing 6-MP, based on the study by Colombel et al. [35]. The studies cited by Winter et al. (2004) ([35], [36], [37]) assume an association of leucopenia with TPMT deficiency of 32%.

Myelosuppression can lead to death. Winter et al. [30] assumed that TPMT screening of 1 000 patients could avoid one death. This suggests that, analysing children who are, on average, 8 years old, and assuming life expectancy of 75 years, screening of 1 000 patients will result in 67 life-years gained, or with a discount of 3%, 29.6 life-years gained.

PCR test

Oh et al. (2004) assumed the sensitivity and specificity of PCR-genotyping to be 96.3% and 100%, respectively. Marra et al. [31] used slightly different estimates for the sensitivity and specificity of the PCR test of 95.2% and 100%, respectively.

Costs

Big differences were found in the material and personnel costs reported for PCR testing by the different countries. The United Kingdom put the cost at GBP 20-30 (EUR 29-44). In Germany

a range from EUR 32 to 300 was reported. For the Netherlands PCR testing was assumed to cost EUR 175, based on the tariffs (NHTA, 2004).[49] In Ireland the estimated cost per test is EUR 250. If the PCR test were in routine clinical use (also for other indications besides ALL, such as rheumatoid arthritis), the estimated costs would be significantly reduced. Other cost-effectiveness analyses reported amounts of CAD 100 (EUR 72 at 2004 prices [31]) and GBP 30 (EUR 44 at 2004 prices [30]).

The costs of adverse events were based on hospital days and outpatient appointments, as other medical costs are minor by comparison. A Dutch expert estimated that 10% of the patients with serious adverse events need inpatient treatment of at least 7 days. In the Netherlands this adds up to EUR 2549 at 2004 prices [38]. The other 90% are treated as outpatients. As they already have frequent outpatient appointments, this will not result in any additional costs. The average cost per patient with an adverse reaction to thiopurine drug treatment in the Netherlands can therefore be estimated at EUR 255.

Winter et al. assumed that in the UK two thirds of patients suffering significant leucopenia could be treated as outpatients, requiring two additional appointments at GBP 115 (EUR 335) at 2004 prices. The remaining patients would require hospital admission because of infective complications. Assuming that they spend 10 days in a haematology ward at GBP 402 a day, this results in a total of GBP 4 020 (EUR 5 863) at 2004 prices for these patients. The average cost per patient can be calculated to be EUR 1 551 (at 2004 prices).

Tavadia et al. [39] reported costs of adverse events in Canada of CAD$ 7 757.69 (EUR 5 578) per case at 2004 prices. Marra et al. [31] assumed that 50% of patients suffering adverse events would need to be hospitalised, for an average of 10 days, at a cost of CAD$ 2 679 (EUR 1 925) at 2004 prices. For the 50% of patients treated as outpatients the costs were assumed to be CAD 790 (EUR 568) at 2004 prices. The average cost per patient totals EUR 1 247. It can therefore be seen that experts are divided over their estimates of the percentage of patients with adverse drug reaction to thiopurine drugs who would need to be hospitalised with the result that estimates of the cost of treating patients with an adverse reaction to thiopurine drugs range from EUR 255 to 1 551 (six-fold difference between the lower and upper estimates). As shown below, the intermediate value of EUR 1 000 per myelosuppression event was used in the cost-effectiveness analysis, and the range of EUR 250 to 1 500 was used for the sensitivity analysis (Tables 3-4 and 3-5 respectively).

Table 3-3: Base case value parameters for the TPMT model

Model parameter	Base case value
Homozygous wild-type	88.7%
Heterozygous	10.0%
Homozygous mutant	0.3%
Probability of myelosuppression	0.03
Adverse events associated with TPMT	32%
Mortality prevented per person screened for TPMT	0.001
Sensitivity of PCR test	95.2%
Specificity of PCR test	100%
Costs of PCR test (EUR at 2004 prices)	150
Costs of myelosuppression (EUR at 2004 prices)	1000

49 NHTA (National Health Tariffs Authority). National Health Tariffs. Utrecht: CTG, 2004.

Base case analysis

Table 3-3 presents the values of the parameters used in the base case model. They are based on the values found in literature and reported by experts, as described above. The base case values are in the middle of the range described for model parameters.

Sensitivity analysis

In the sensitivity analysis the values of the model parameters are varied, in order to determine the influence each parameter has on cost-effectiveness. The lower and upper values are based on the values for the parameters found in literature and reported by experts, as described above. The lower and upper values are the lower and upper bounds of the range described for model parameters (see Table 3-4).

Results

Base case analysis

The cost-effectiveness analysis was performed for a hypothetical cohort of 100 000 children with ALL. Out of these 100 000 children, 3 000 will suffer myelosuppression (of which 960 cases are related to TPMT deficiency) and 100 will die as a consequence. Assuming a sensitivity of the PCR test of 95.2%, it would be possible to prevent 914 of these adverse events by screening for TPMT prior to initiation of 6-MP treatment.

The savings due to the prevention of adverse events total EUR 931 920, while the cost of PCR tests for 100 000 children with ALL are EUR 15 000 000, indicating the cost of TPMT screening to be EUR 141 per child with ALL.

If one death were avoided per 1 000 children screened, 100 children would be saved, i.e. 6 700 life-years would be saved by screening 100 000 children, costing EUR 2 102 per life-year saved. When discounted at 3%, the cost rises to EUR 4 760 per life-year saved. Consequently, TPMT testing in children with ALL appears to be highly cost-effective.

Sensitivity analysis

In a univariate sensitivity analysis one variable was varied at a time (see Table 3-5). Taking the lower values for the probability of myelosuppression, for adverse events associated with TPMT, for mortality prevented per person screened for TPMT, for the sensitivity of the PCR test and for the costs of myelosuppression produces a less favourable cost-effectiveness ratio. Although the changes in the cost-effectiveness ratio were small for most of the parameters, the costs per life year gained increased considerably if the lower value is taken for the mortality prevented per person screened for TPMT. In contrast to the other parameters, lowering the costs of the PCR test leads to a more favourable cost-effectiveness ratio.

Table 3-4: Lower and upper values of parameters for the TPMT model

Model parameter	Sensitivity analysis	
	Lower	Upper
Probability of myelosuppression	0.01	0.1
Adverse events associated with TPMT	20%	50%
Mortality prevented per person screened for TPMT	0.0001	0.003
Sensitivity of PCR test	76.2%*	99.9%*
Costs of PCR test (EUR at 2004 prices)	30	300
Costs of myelosuppression (EUR at 2004 prices)	250	1500

* *Marra et al. 2002*

Table 3-5: Univariate sensitivity analysis: cost-effectiveness ratio, expressed as costs per life-year gained

Model parameter*	Lower value	Upper value
Probability of myelosuppression	4.965	4.039
Adverse events associated with TPMT	4.875	4.615
Mortality prevented per person screened for TPMT	47.596	1.587
Sensitivity of PCR test	4.821	4.744
Costs of PCR test	705	9.829
Costs of myelosuppression	4.991	4.605
Baseline	4.760	

** For lower and upper values of model parameters, with 3% discounting.*

In multivariate sensitivity analyses all model parameters included in the sensitivity analysis (see Table 3-4) were varied together. Assuming that all the model parameters mentioned in Table 3-4 are independent from each other, a set of extreme parameter values can be constructed that yield the highest and the lowest cost-effectiveness ratios. To construct the highest (least favourable) cost-effectiveness ratio, the lower values were taken for the probability of myelosuppression, for the percentage of adverse events associated with TPMT, for the mortality prevented by TPMT screening and for the costs of myelosuppression. For the costs of the PCR test, the upper value was taken. This resulted in a cost-effectiveness ratio of €44 719 per life-year saved (€101 240, with 3% discounting). At the opposite extreme, the upper values for the probability of myelosuppression, for the percentage of adverse events associated with TPMT, for the mortality prevented by TPMT screening and for the costs of myelosuppression combined with the lower value for the costs of the PCR test produced both financial savings and a gain in life-years. In this context it is important to keep in mind that genotyping costs are expected to decline in future, and could be driven down further by high testing rates.

3.4.3 HER2

Model parameters were identified and searched for in the literature and from experts in each country.

Percentage of women with HER2 overexpression

About 20 to 30% of all women with metastatic (late stage) breast cancer have an overexpression of HER2 receptors on the surface of the breast cancer cells [40, 41] and therefore qualify for treatment with trastuzumab (Herceptin).

Prognosis of metastatic breast cancer

In the model four groups of women with metastatic breast cancer can be distinguished: HER2-positive women receiving chemotherapy alone, HER2-positive women receiving chemotherapy plus trastuzumab, HER2-negative women receiving chemotherapy alone and HER2-negative women receiving chemotherapy plus trastuzumab. The fourth group entails a needless waste of public healthcare resources, since patients who are HER2-negative gain no benefit from trastuzumab treatment. Moreover, they are needlessly exposed to potential adverse effects of such treatment. HER2 testing must therefore give high priority to avoiding false positives. The median survival of women with metastatic breast cancer who are HER2-negative and receive chemotherapy (paclitaxel) was found to be 27.5 months (95% CI = 17.1 to 35.2 months) by Konecny et al [42]. In a randomised trastuzumab trial almost equivalent response rates were found among patients with a negative FISH result [43, 44]. Therefore, it was assumed that trastuzumab provided no additional benefit in HER2-negative women [45].

Table 3-6: Test-treatment strategies for women with metastasised breast cancer

Strategy	Initial test	Confirmatory test	Treatment
1	IHC	None	Chemotherapy + trastuzumab if IHC 3+Chemotherapy otherwise
2	IHC	None	Chemotherapy + trastuzumab if IHC 2+Chemotherapy otherwise
3	IHC	FISH if IHC 2+ or IHC 3+	Chemotherapy + trastuzumab if FISH+Chemotherapy otherwise
4	IHC	FISH if IHC 2+	Chemotherapy + trastuzumab if FISH+Chemotherapy + trastuzumab if IHC 3+Chemotherapy otherwise
5	FISH	None	Chemotherapy + trastuzumab if FISH+Chemotherapy otherwise
6	None	None	Chemotherapy + trastuzumab for all

Slamon et al [46] estimated the median overall survival in women with HER2-positive tumours treated with chemotherapy to be 18.4 months. This estimate is within the 95% CI for survival found by Konecny et al. [42] (15.3 to 27.3 months). Addition of trastuzumab to treatment was associated with longer overall survival (median 22.1 months, [46]). On average trastuzumab treatment therefore prolongs life by only 3.7 months for these HER2-positive patients.

Quality of life

Osoba et al [47] studied the effects on quality of life of combining trastuzumab with chemotherapy in women with metastatic breast cancer. They found no significant improvement in quality of life for patients on chemotherapy plus trastuzumab compared to those on chemotherapy alone.

Earle et al. [48] performed a systematic review of cost-utility assessments in oncology. They reported the utility value for metastatic breast cancer in different age groups as between 0.16 and 0.85.

Tests

Elkin et al. [45] identified ten studies that compared the IHC test (HercepTest, DAKO) with FISH, used in accordance with the manufacturer's instructions, on a series of unselected cases and reported results in adequate detail. On the basis of these studies, they calculated the average test characteristics, with each study's estimate weighted by the respective sample size of FISH-positive and FISH-negative cases. They assumed that the FISH test was a gold standard for HER2 status. The different HER2 test-treatment strategies and the results for IHC compared with FISH testing are presented in Table 3-6 and Table 3-7 respectively.

Costs

The reported costs of the IHC test (including material and personnel costs) vary significantly, from GBP 70 (EUR 103) in the United Kingdom to EUR 190 in Ireland. Intermediate values were reported by Germany: EUR 127 (public institutions) and EUR 167 (private institutions). For the Netherlands only the material costs have been reported (EUR 30). In the literature lower costs are quoted: USD 85 (EUR 68 at 2004 prices [45]) and DEM 188 (EUR 102 at 2004 prices [49]).

The same differences are seen in the reported costs of the FISH test (including material and personnel costs) which vary between GBP 150 (EUR 220) in the United Kingdom to EUR 495 in

Table 3-7: HercepTest (IHC) characteristics compared with FISH [95% confidence interval (CI)]

	IHC 0/1+	IHC 2+	IHC 3+
FISH+	0.079 [0.025, 0.134]	0.250 [0.168, 0.332]	0.671 [0.547, 0.795]
FISH -	0.843 [0.779, 0.908]	0.140 [0.081, 0.200]	0.017 [0.004, 0.029]

the Netherlands. The reported costs from Ireland (EUR 250) and Germany (EUR 257 for public institutions and EUR 398 for private institutions) are within this range. In the literature the costs of the FISH test are put at USD 382 (EUR 292) [45] and DEM 150 (EUR 82) at 2004 prices [49].

The additional costs of treating women with metastasised breast cancer with chemotherapy plus trastuzumab instead of chemotherapy alone consist of direct medical costs (cost of treatment with trastuzumab) and non-medical costs (for example, patient time costs, travelling costs, cost of sick leave). It was beyond the scope of this study to estimate the additional non-medical costs which would be required for an economic analysis from the societal perspective. This study therefore restricted the additional cost of treating women with chemotherapy plus trastuzumab instead of chemotherapy alone to the direct medical costs.

In the Netherlands the additional costs are reported to consist of an average of six three-week courses of treatment with trastuzumab. One course of treatment with trastuzumab costs EUR 656, assuming a mean weight of 75 kg (Health Care Insurance Board, 2005[50]). Patients are also given dexamethason against side-effects of trastuzumab. Dexamethason costs EUR 22 per treatment (8 ml). Every first week of a course of treatment consists of chemotherapy plus trastuzumab and then in the second and third weeks only trastuzumab is administered. This means that 12 additional outpatient appointments are needed for treatment with chemotherapy plus trastuzumab compared to chemotherapy alone. Each outpatient appointment costs EUR 72 [38]. The resulting additional medical costs (clinic appointments plus drugs) total EUR 13 068.

In the United Kingdom, after loading, 8 to 20 cycles of trastuzumab are administered to the patient. According to expert opinion trastuzumab costs GBP 400 (EUR 589) per treatment. Assuming an average of 15 treatments, trastuzumab costs a total of GBP 6 000 (EUR 8 842). This is in the same order of magnitude as the GBP 5 296 (2000 prices) and GBP 4 235 (2003 prices) reported by Lewis et al. [50] and the Department of Public Health (2004) respectively.[51] Furthermore, an echocardiogram is taken every 12 weeks. For an average of four echocardiograms at GBP 89 (EUR 133) per echocardiogram at 2004 prices (Department of Health, 2004), this adds up to EUR 531. The additional medical costs in the United Kingdom total EUR 6 531 (excluding outpatient clinic appointments).

Results

Base case analysis

The cost-effectiveness analysis was performed for a hypothetical cohort of 100 000 women with metastasised breast cancer for the strategies listed in Table 3-6. The results are presented in Table 3-8.

Also the costs and effects of the different treatment strategies were compared with the costs and effects of the baseline strategy (in which all women receive chemotherapy) in Figure 3-3. It can be concluded from Figure 3-3 that only strategy 3 (use FISH as confirmation of all positive IHC results) and strategy 5 (use FISH alone) are efficient. These are the two strategies for which no alternative policy gains more life-years at lower costs. The incremental cost-effectiveness of strategy 3 compared to the baseline strategy totals EUR 90 500 per QALY gained. Strategy 5 will result in a gain of 609 QALYs per 100 000 women with metastasised breast cancer compared with strategy 3, but at additional costs of EUR 29 million. This gives an incremental cost-effectiveness ratio of EUR 95 200 per QALY gained for strategy 5 compared with strategy 3.

See Table 3-6 for a cohort of 100,000 women with metastasized breast cancer compared to a strategy in which all women receive chemotherapy

50 Health Care Insurance Board. Pharmacotherapeutical Compass. Amstelveen: Health Care Insurance Board, 2005.
51 Department of Health. NHS Reference Costs 2003 and National Tariff 2004 ("Payment by Results Core Tools 2004"). 2004.

Table 3-8: Costs (euros) and effects of the different treatment strategies (see Table 3-6) for a cohort of 100 000 women with metastasised breast cancer (2004 prices, no discounting)

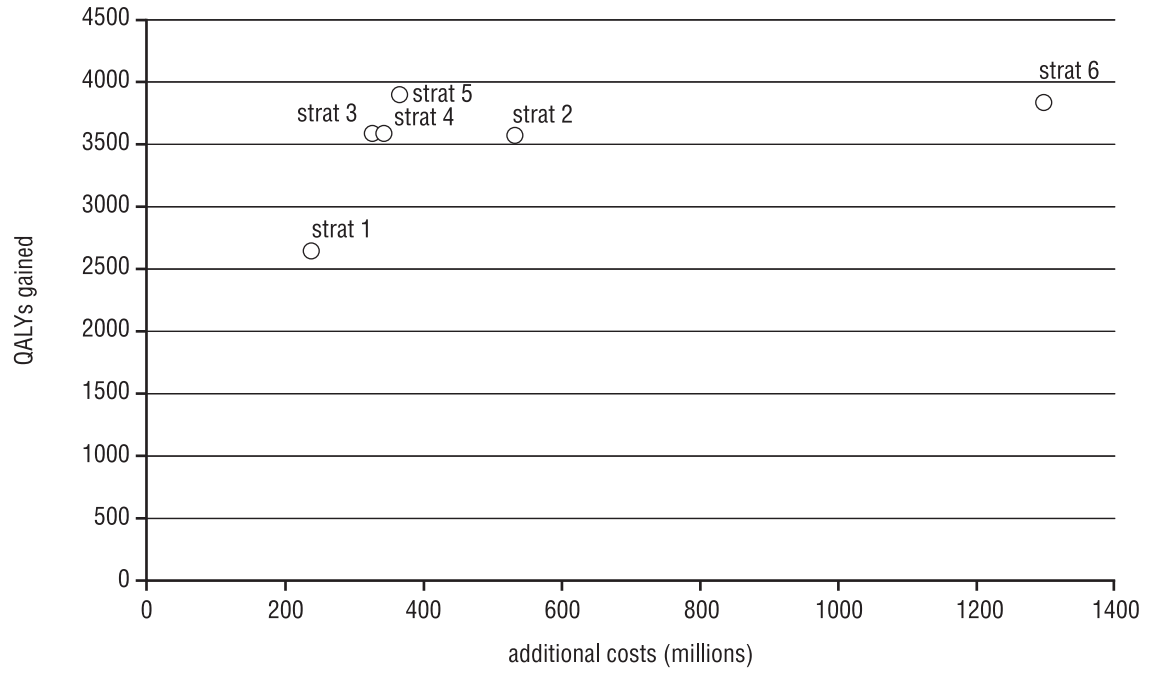
	Baseline*	1	2	3	4	5	6
Costs of initial testing (millions)	0	13	13	13	13	25	0
Costs of confirmatory testing (millions)	0	0	0	9	17	0	0
Additional treatment costs ** (millions)	0	235	452	299	299	325	1300
Total additional costs (millions)**	0	248	465	321	330	350	1300
Life-years	210.208	215.381	217.308	217.308	217.308	217.917	217.917
QALYs	105.104	107.690	108.654	108.654	108.654	108.958	108.958
Cost per life-year gained**		47 900	65 600	45 200	46 400	45 400	168 700
Cost per QALY gained**		95 800	131 100	90 400	92 800	90 800	337 300

** All women with metastasised breast cancer receive chemotherapy; see Table 3-6 for the various HER2 screening strategies.*
*** Compared with the baseline strategy.*

Sensitivity analysis

In a univariate sensitivity analysis one variable was varied at a time. Taking the lower values for the percentage of metastasised breast cancer patients with HER2 overexpression, the probability of IHC 2+ test results in FISH+ women and the probability of IHC 3+ in FISH+ women produces a less favourable cost-effectiveness ratio. For the probability of IHC 2+ test results in FISH-negative women, the probability of IHC 3+ test results in FISH-negative women, the costs of the IHC test, the costs of the FISH test and the additional medical costs of treatment with trastuzumab, lower values produce a more favourable cost-effectiveness ratio. Varying the median survival leads to differences in the expected cost-effectiveness ratio, if the difference in median survival between women treated with

Figure 3-3: Costs and effects of different treatment strategies



and without trastuzumab changes. If the difference in median survival between women treated with and without trastuzumab is reduced, the cost-effectiveness ratio of HER2 testing becomes less favourable.

A probabilistic multivariate sensitivity analysis assumed a uniform distribution for the parameters between the lower and upper values in Table 3-9.

The most important parameters determining the variance in cost-effectiveness are the median survival estimates, the additional costs of treatment with chemotherapy plus trastuzumab compared with chemotherapy alone, and the quality of life of women with metastatic breast cancer.

This study analysed two examples of pharmacogenetic testing: HER2 testing (efficacy of trastuzumab) in women with metastatic breast cancer and TPMT testing (safety of thiopurine drugs) in children with ALL.

For both applications an exploratory cost-effectiveness review was performed by developing models for comparison of the costs and effects of the pharmacogenomic treatment strategy with current medical practice. For the four participating countries (Germany, Ireland, the United Kingdom and the Netherlands), information on model parameters was collected from literature and experts.

The exploratory analysis on TPMT testing in children with ALL revealed an expected cost-effectiveness rate of €4 760 per life-year gained (3% discounting). Phillips and Van Bebber [1] assume intervention to be favourable if the cost-effectiveness rate is lower than US$ 50 000. The base case estimate for TPMT testing in children with ALL compares favourably with this threshold.

The sensitivity analysis established that the maximum cost per life-year gained, given the range of parameter values that seems plausible, is €101 240, but TPMT could also lead to both financial savings and a gain in life-years.

For a more definitive estimate of the cost-effectiveness of TPMT testing in children with ALL, further research on the costs of the PCR test and the mortality prevented by TPMT screening is a high priority, as these are the model parameters which had the greatest influence on the variance in cost-effectiveness. As mentioned earlier, screening costs are expected to be substantially reduced if the TPMT test were to become more widespread, as the current high test costs partly reflect the low level of use.

The analysis of HER2 testing in women with metastatic breast cancer shows that use of the FISH test to confirm all positive IHC results and use of the FISH test alone are efficient strategies. This favourable role played by the FISH test can be explained by the high costs of Herceptin treatment, the limited effectiveness of Herceptin and, even then, only in HER2-positive women, and the capability of the FISH test to avoid false-positive screening results (and unneeded Herceptin treatment). It is therefore not surprising that the study by Elkin et al. [45] came to the same conclusions and that the results were confirmed by the sensitivity analysis.

The costs per QALY gained, however, are relatively high for the efficient strategies. The incremental cost-effectiveness ratio is expected to be €90 500 per QALY gained if the FISH test is used to confirm all positive IHC results compared with no treatment with Herceptin, and €95 200 per QALY gained for FISH alone compared with IHC testing followed by FISH confirmation of 2+ and 3+ results. Based on the assumption by Phillips & Van Bebber [1] that intervention is favourable if the cost-effectiveness rate is lower than US$ 50 000, it could be concluded that the cost-effectiveness of use of Herceptin is unfavourable. However, this depends on current practice. This analysis assumed treatment without Herceptin to be current practice. If Herceptin is used in clinical practice in a country without any HER2 testing, FISH testing will be cost-effective.

Note that cost/benefit ratios for HER2 testing might become far more favourable if Herceptin is later approved for early-stage cancers. So far Herceptin treatment, and therefore also HER2 testing, have been confined to late-stage disease. If Herceptin is found to prolong life significantly longer when used at an early stage (clinical trials on this are under way), this could drastically improve cost/benefit ratios for HER2 testing. In October 2005 the UK government decided, in response to pressure from patients' groups, also to allow women with early-stage breast cancer access to trastuzumab [51], a scenario which might have dramatic effects on the cost-effectiveness analysis presented in this report. Further studies are needed on the medical benefit of trastuzumab in early-stage cancers before a cost-effectiveness analysis can be applied.[52]

The median survival of women with metastatic breast cancer for the different treatment strategies, the additional costs of trastuzumab and the quality of life of women with metastatic breast cancer are the parameters that have high priority in further research on the cost-effectiveness of HER2 testing in women with metastatic breast cancer.

In conclusion, this exploratory study has provided information on the expected cost-effectiveness of HER2 testing in women with metastatic breast cancer and TPMT testing in children with ALL and identified the parameters that need to be estimated more accurately to give a more definitive estimate of the cost-effectiveness of these two pharmacogenomic strategies.

This kind of exploratory study combining evidence available from literature with expert opinions is useful for prioritising cost-effectiveness research on pharmacogenomic strategies and identifying which model parameters should be included in further research on the cost-effectiveness of this pharmacogenomic strategy, preferably in a prospective study using standardised methods.

3.5 Conclusions

- Clarifying the economic implications of pharmacogenomic treatment strategies is important, as this could facilitate implementation of such strategies.
- Cost-effectiveness analyses of applications of pharmacogenomics are sparse.
- Data are scarce for studying the cost-effectiveness of TPMT testing (safety of thiopurine drugs) in children with acute lymphoblastic leukaemia.
- Large differences in costs are reported between countries.
- TPMT testing in children with ALL shows a favourable cost-effectiveness ratio.
- FISH alone or FISH as a confirmative test after an IHC positive result are preferable strategies for HER2 testing in women with metastasised breast cancer.

3.5.1 Limitations

There are a number of limitations to this cost-effectiveness study. Models are always a simplification of reality. Sometimes, the abstraction made in this study is quite rough due to the time-frame and more sophisticated models might be more appropriate to obtain estimates on cost-effectiveness. However, the results on the cost-effectiveness of HER2 testing were in line with the results of a more sophisticated model on this subject [45]. Apart from this uncertainty about the model, the study is also subject to uncertainty about the parameters. The model parameters are based on a review of the literature and expert opinions. Some of the information was not available for the participating countries, and estimates for model parameters for other situations taken from the literature were used.

52 Trastuzumab plus chemotherapy improves survival in early-stage HER2-positive breast cancer patients. Oncology (Williston Park). June 2005;19(7):851, 862.

For the TPMT study hardly any information was available specifically for children with ALL. Therefore, estimates from pharmacoeconomic studies on other thiopurine drugs were frequently used. Some of the estimates for the model parameters are based on information from experts.

To explore the role of parameter uncertainty, sensitivity analyses were performed, in which the influence of changes in each of the model parameters is investigated separately. In this way, it can be inferred how the cost-effectiveness estimate will change, if further research on a model parameter were to produce an estimate differing from the one used in the base case analyses. Further research on model parameters, preferably in a prospective study using a standardised method, is warranted, especially for the TPMT model.

4. Regulatory framework

As the governance processes surrounding PGx and related fields such as genetic testing are still emerging, there are few legal requirements at national or international level influencing their use. However, pre-existing legislation, rules and codes of practice, monitored by government, professional organisations and at local and laboratory level are often relevant to the application of PGx. A broad interpretation of regulation has therefore been applied here to provide policymakers with a wide-ranging view of measures that can be used to influence positively the performance of PGx technology in society. Pragmatically this means that the regulatory framework described here includes a wide range of factors influencing:

- The development and licensing of drugs;
- The development and licensing of diagnostics for marketing;
- The development of diagnostics services (including "home brews");
- Oversight of laboratory practices, including staff training, quality control and quality assurance;
- The clinical guidance for doctors, nurses and pharmacists on use of PGx tests and the implications of their results;
- Wider legal frameworks, such as those addressing genetic discrimination.

The Wp3 report (www.jrc.es) contains detailed case study reviews of the current status of regulation for each of the above regulatory elements in the USA and four EU Member States (Germany, Ireland, the Netherlands and the UK). Here only the US case study is discussed in full as an illustration of how the above regulatory elements form a bench-to-bedside system that must be regarded as a whole. Many of the same issues are explored in the case of other countries. In technological terms the USA may be regarded as more advanced with adoption of PGx technology. Its governance of laboratory testing, and legislative preparation for genetic test use in society, may also be regarded as more advanced in some respects – although new regulations are still in preparation. The US case study is followed by a comparison of EU-level regulations and review of regulatory themes in selected Member States, where these differ significantly from the US case. The final section of this chapter provides cross-cutting assessments of these frameworks by respondents from industry. Table 4-1 at the end of this chapter provides a quick-reference summary of key points from the national case studies.

4.1 Regulatory frameworks for PGx in the USA

There are three relevant government institutions involved in oversight of PGx, all contained in the Department of Health and Human Services. The Food and Drug Administration (FDA) oversees drug and device licensing, including diagnostic test kits and reagents. The Center for Disease Control (CDC) has a public health focus, its Division of Laboratory Services develops guidelines and policies for diagnostic testing and the Centers for Medicare and Medicaid Services administer regulatory management of laboratory services and their reimbursement.

Policy with regard to the use of genetics in healthcare has also been shaped substantially in recent years by the activities of the National Institutes of Health (NIH) and Department of Energy, following their investments in the Human Genome Programme.

A report on the context of genetic testing in the USA, commissioned by the NIH-Department of Energy working party on ethical, legal and social implications of human genome research in 1995 and published in 1998, highlighted the need for greater regulatory oversight of genetic

testing services [52]. Following this, in 1998 the Clinical Laboratory Improvement Advisory Committee (CLIAC) in the CDC recommended that the Clinical Laboratory Improvements Act (CLIA) should be updated to establish specific regulations to address genetic testing, and in 1999 the Department of Health and Human Services Secretary's Advisory Group on Genetic Testing (SACGT - formed on the recommendation of the 1998 Holtzman and Watson report [52]) in turn called for greater oversight. However, to date no new regulation has been agreed, although the CDC is developing new guidelines.

High expectations still surround pharmacogenetic testing in the USA. In particular, policy circles promise significant change within a decade,[53] and at the National Human Genome Research Institute scenarios are even being discussed where pharmacogenetics could make the difference between an individual dying at 50 and living to well over 100.[54]

Hopes for personalised medicine are also being actively promoted in the USA by a lobby group called the Personalised Medicine Coalition (PMC), although it more cautiously notes that these developments will take time:

"Personalised medicine is poised to transform healthcare over the next several decades. New diagnostic and prognostic tools will increase our ability to predict the likely outcomes of drug therapy, while the expanded use of biomarkers — biological molecules that indicate a particular disease state — could result in more focused and targeted drug development. Personalised medicine also offers the possibility of improved health outcomes and has the potential to make healthcare more cost-effective." (PMC website)

The PMC was established to provide opinion leadership, a channel for education and a forum for discussion and consensus.[55] It appears to be primarily industry-driven and has a broad membership, which includes representatives of government agencies, universities, professional and industry associations, large pharma and biotech firms.[56] The views of the PMC appear to be echoed in the Department of Health and Human Services advisory circles where there are also high hopes of PGx (policy 2).

4.1.1 Regulation of PGx tests and PGx in drug development

As already mentioned, the agency responsible for drug regulation in the USA is the FDA. It consists of a number of Centers, with the largest, the Center for Drug Evaluation and Research (CDER), being responsible for ensuring the safety, efficacy and quality of medicines prior to marketing, and for post-marketing surveillance. Marketing approval for a new product is obtained by submission of a New Drug Application (NDA), and approval for clinical trial use is obtained via an Investigational New Drug application (IND).

Marketed diagnostic tests are subject to regulatory review by the Office for In Vitro Diagnostics (OIVD) within the Center for Devices

53 "During the next decade, the practice of medicine will change dramatically through genetically based diagnostic tests and personalised, targeted pharmacologic treatments that will enable a move beyond prevention to preemptive strategies" - Senator Bill Frist, Annual Shattuck Lecture of the Massachusetts Medical Society, 2004. Cited by Francis Collins – see final slide at: http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf.

54 http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf.

55 http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.asp.

56 PMC members listed in April 2005 include: Abbott Laboratories Inc., Affymetrix Inc., American Clinical Labs Association, Amgen Inc.Centers for Disease Control and Prevention, Center for Medicare and Medicaid Services, dnaprint genomics Inc., Duke University, Feinstein Kean Healthcare, Genaissance Pharmaceuticals Inc., Gene logic, Genentech Inc. Genetic Alliance, Genetics & Public Policy Center Genomas Inc. Genomic Health Inc., Genzyme Inc., Harvard Medical School-Partners Healthcare Center for Genetics and Genomics, IBM Corporation, Millennium Pharmaceuticals Inc., the National Cancer Institute, The National Human Genome Research Institute, Pathway Diagnostics, Perlegen Sciences, Pfizer Inc., PhRMA, Princeton Group International Inc, Procognia Inc., Qiagen Inc., Siemens Inc., Theranos Inc, U.S. Food and Drug Administration, and Virologic.

and Radiological Health (CDRH) – in contrast to other countries where no pre-market review is undertaken. However, tests developed by clinical laboratories for "in-house" use are not regulated by the FDA and are subject to less stringent controls, as described in more detail below.

The US drug regulation system evolved throughout the 20th century. Congress passed the Orphan Drug Act 1983 to provide incentives to companies to conduct research and development work on medicines for disorders that affect fewer than 200 000 sufferers. The most powerful incentive introduced by the Act was marketing exclusivity.[57] According to several commentators, similar legislation may be necessary to encourage the equitable development of PGx technology [10, 53].

The most important recent changes and reforms are encapsulated in the 1997 FDA Modernization Act, and the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. During the 1990s additional resources were provided by the US Congress, and the Prescription Drug User Fee Act of 1992 was negotiated with the pharmaceutical industry, signalling a shift to a "user fee" structure in place of government funding for review activities. As part of the deal, the CDER agreed to review priority new drugs in six months or less and standard new drugs in a year or less. The result was that review times were cut significantly, mirroring similar changes in Europe and elsewhere during this period. Many of these reforms, plus new targets to further shorten review times and various other goals such as improving communication, were consolidated in the FDA Modernization Act and the Prescription Drug User Fee Act, which became law in 1997.

Diagnostic devices

The MDUFMA introduced a number of significant features to the procedure for pre-market review of devices, including: user fees and performance goals for many types of pre-market reviews, with these goals becoming more demanding over time; and establishment of the Office for Combination Products (OCP) which is discussed below. The Act also introduced new regulatory requirements for reprocessed single-use devices, including a new category of pre-market submission, the pre-market report.[58]

As described above, marketed diagnostics, including PGx tests, are subject to FDA review, whereas diagnostic tests developed by clinical laboratories – "home brews" or "lab-developed tests" (the term preferred by US commercial laboratories) – are not subject to formal review by the Agency.[59] The sole regulatory framework applicable to tests provided through laboratories is compliance with standards laid down by the Clinical Laboratory Improvement Amendments (CLIA) regulations.

Regulating combinations of drug and diagnostic device

The FDA's Office of Combination Products (OCP) is also relevant to the US regulatory environment for PGx because the Agency views such products as combination products. Combination products include drug-device, drug-biologic and device-biologic products and are increasingly incorporating novel technologies that hold promise for advancing patient care.[60] Essentially, a range of technological

57 Once the FDA approves a company's product for a designated orphan disease, competitors are legally blocked from introducing an identical competing product for seven years. Other provisions provide grants, help from the FDA in designing research protocols that will meet regulatory requirements, and tax credits.

58 The MDUFMA also introduced inspections of device manufacturers by accredited third parties, under carefully prescribed conditions (http://origin.www.fda.gov/cdrh/mdufma/mdufmasummary.html#1. Accessed on 23.4.2005.

59 Clinical testing laboratories in the USA are usually commercial operations, but a number of non-profit institutions, such as the Mayo Clinic, also provide diagnostic services, including PGx tests.

60 Typical examples of combination products include improved drug delivery systems, drug eluting stents and drug-biologics that, when used in combination, may potentially enhance the safety and/or effectiveness of either product used alone. Biologics are also being incorporated into novel orthopedic implants to help facilitate regeneration of bone required to permanently stabilise the implants.

developments, including pharmacogenetics, are blurring the historical dividing lines between FDA centers. According to the FDA, this blurring of responsibilities has raised "challenging regulatory, policy and review management issues" since combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers.[61]

In addition, the FDA has recognised criticisms regarding the Agency's approach to regulating combination products, including: "concerns about the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the post-market regulatory controls applicable to combination products; and lack of clarity regarding certain Agency policies, such as when applications to more than one Agency Center are needed."[62]

The OCP was established in 2002 to address these concerns, as required by the MDUFMA of 2002. The 2002 Act gives the Office broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic and device-biologic combination products. However, the primary regulatory responsibilities for, and oversight of, specific combination products remain with one of the three product centers to which they are assigned - the CDER, the CDRH and the CBER (Center for Biologics Evaluation and Research).

The OCP is likely to play a coordinating role in the PGx approval process, but the extent and nature of this involvement is still unclear.[63] However, while the OCP operates within the legislative and institutional structures of US drug regulation, given the increasingly globalised pharmaceutical market and harmonised regulatory framework, many of the issues relevant to management of combination products in the USA are likely to be applicable to other regions, including the EU.

Use of PGx data in drug approval

The FDA shapes the drug approval process by interpreting and enforcing the legislative provisions laid down in the FD&C Act by means of issuing federal regulations (US Code of Federal Regulations, CFR). Federal regulations are supplemented by guidances, which are not legally binding but are intended to provide guidance on methods or current FDA thinking on specific topics. Guidance documents have been instrumental in shaping the FDA approach to PGx.

The most important FDA guidance document to date with regard to PGx is the Pharmacogenomics Guidance, which after a series of drafts published over the past three years, was finally released in March 2005. The Guidance clarifies which PGx data are required to be submitted and which data the Agency would like to have submitted under the FDA Voluntary Genomic Data Submission (VGDS) programme. Another important FDA document recently released is the Concept Paper on Co-Development. This explores possible approaches to co-development and regulatory submission of data for approval of a drug and diagnostic.

The FDA published its long-awaited Concept Paper on drug-diagnostics co-development in April 2005. Coordination of the drug-test protocol

61 http://www.fda.gov/oc/combination/overview.html. Accessed on 21.4.2005.
62 http://www.fda.gov/oc/combination/overview.html. Accessed on 21.4.2005.
63 OCP duties include: "assigning an FDA Center to have primary jurisdiction for review of a combination product; ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one agency center; ensuring consistency and appropriateness of postmarket regulation of combination products; resolving disputes regarding the timeliness of premarket review of combination products; updating agreements, guidance documents or practices specific to the assignment of combination products; submitting annual reports to Congress on the Office's activities and impact." The OCP is also working with FDA Centers "to develop guidance or regulations to clarify the agency regulation of combination products […] and serving as a focal point for combination products issues for internal and external stakeholders." (http://www.fda.gov/oc/combination/overview.html).

is viewed by the Agency as crucial to successful and timely approval of PGx products. Previous examples suggest that this has not been done very successfully in the past. Among the key concerns are timing and communication within and between Centers, so that reviewers in different parts of the Agency benefit from others' expertise and from better coordination of the overall review process.

The second area of concern has been the question of biomarker definition and validation. The key questions are what constitutes a biomarker, and how to define the difference between a known, or probable, biomarker and an exploratory biomarker. These classifications dictate the type of data required to be submitted to the Agency and the data that may be voluntarily submitted under the VGDS scheme. In part, the current lack of clarity over the difference between "probable" and "exploratory" biomarker arises from tension between the science and regulatory demands [54]. These definitional problems are considered minor obstacles compared to the challenge posed by the practical need to validate a "probable biomarker" scientifically. In other words, sponsors must ensure that the appropriate science has been conducted to call a biomarker a "probable biomarker" before submitting such data as part of a required submission such as an NDA or IND application.

One significant finding that emerged from a joint FDA-industry workshop held in 2003 was that industry and US regulators hold markedly different ideas on what constitutes an "exploratory" and a "valid" biomarker, with the FDA adopting a much more cautious approach than industry. Joint examination of case studies found that compared to industry the FDA considered far more data "voluntary" (i.e. exploratory in nature) rather than "required".

Clinical trial data obtained from stratified populations might change the approach adopted by regulators towards such data. For example, will regulators demand safety data from the whole population or be willing to accept data based on a stratified sub-population? According to the FDA, the time taken and the cost for the sponsor might be improved. In general, it is much easier to obtain approval if data from a stratified population show better efficacy in that population or group, compared to looking at the overall population. Oncology provides a particularly good example, because in cases where 10 to 15% efficacy is demonstrated overall, the potential impact on development time and costs is huge if responders to treatment can be identified and the trial can then be run on that sub-population.

One area where concern has been expressed is the possibility that some section of the population will be excluded from targeted medicines – the "orphan patient" scenario. A senior staff member at the UK MHRA, for example, expressed the view that this was a potential problem for society as a whole, although it was unclear whether regulatory authorities either would, or should, have a role in decisions related to this issue. In the US context, however, the FDA respondent did not feel this was likely to be a major issue as companies could utilise existing orphan drug legislation. Alternatively they might use the accelerated approval process available in the USA for drugs directed at unmet medical needs. For example, the "unmet needs" criterion could be met by developing a drug for a sub-population identified as non-responders to a certain therapy which would then qualify for accelerated approval status, which offers a much more friendly regulatory environment.

Do regulatory frameworks encourage PGx in drug development?

The FDA's intent is to encourage PGx development and it has demonstrated this by publishing the PGx guidance document and related guidances and providing the regulatory framework needed to bring this about. However, as this framework has only just been established, it is too early to measure how successful it will be. The FDA hopes that now that the guidance document is published, industry's concerns have been addressed by the Agency, although legitimate questions will arise in the future, because it is not possible to foresee all possible scenarios.

One relevant question is whether information submitted voluntarily could ever have an impact on the formal assessment process. Clearly, if regulators see a safety issue, they cannot ignore it. VGDS is called "voluntary submission" because the responsibility is on the company to decide what to submit. However, to separate the two types of data review within the Agency and to build trust on the part of industry, individual reviewers of voluntarily submitted data will not be involved in subsequent formal reviews for the same entity.

A regulatory perspective on the expected impact of PGx

The expectation is that many submissions in years to come will include PGx data, as virtually every development programme in major companies has some genomic component. Indeed, there is scepticism within the Agency that the traditional blockbuster model of drug development can continue. There is a strong belief that future development will inevitably be directed at more targeted medicines – "a blockbuster for a sub-population" – with the possibility of "niche" products for smaller markets also being developed by smaller companies.

The FDA's views on the part PGx will play in pharmacovigilance are probably more cautious. The FDA respondent again suggested that the issue can best be examined in terms of its scientific and non-scientific aspects. Following a drug's approval, its first few years on the market are akin to a larger clinical trial and there will inevitably be unforeseeable adverse events. That leaves the question whether it would be possible to develop PGx tools that would identify people who are at higher risk of adverse reactions, possibly by re-contacting them and studying their genotypes.

The FDA is enabling use of PGx in drug development through initiatives like the Pharmacogenomics Guidance document discussed above, and initiating reviews of product labels of approved drugs in appropriate cases. There are no barriers to including PGx-related information on labels. Herceptin is the best-known example, but around 35% of US-approved drugs have PGx information on the label [55].

In legislative terms, if additional evidence is available, US federal law empowers the Agency to describe this evidence and identify specific tests for selecting and monitoring patients who need the drug.[64]

Recent examples include 6-mercaptopurine and TPMT, where the existing label has been revised in conjunction with the sponsors to inform clinicians about the option of using TPMT testing to guide treatment with 6MP. In the case of the colorectal cancer drug irinotecan (Camptosar, Pfizer), the absence of PGx information on the label, in spite of growing evidence of a link between a specific UGT1A1 allele and risk of severe toxicity, was highlighted in 2004. Although insufficient evidence is presently available to recommend exact dosing according to genotype, the label was recently changed to reflect the increased risk of neutropenia for individuals with the relevant genetic profile [55].

4.1.2 Regulation of PGx services – from the laboratory to the clinic

Formal regulation of testing services is centred on the Clinical Laboratories Improvement Amendments (CLIA) passed by the US Congress in 1988. The most recent CLIA regulations were published in February 1992 and are based on the complexity of the test method: the more complicated the test, the more stringent the requirements.[65]

64 Code of Federal Regulations, 21 CFR 201.57. Specific requirements on content and format of labelling for human prescription drugs (revised 2001). Available at: http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html. Accessed on 22.6.2005.

65 Three categories of tests have been established: waived complexity, moderate complexity, including the subcategory of provider-performed microscopy (PPM), and high complexity.

CLIA specify quality standards for proficiency testing (PT), patient test management, quality control, personnel qualifications and quality assurance for laboratories performing moderately and/or highly complex tests. Waived laboratories must enrol in CLIA, pay the applicable fee and follow manufacturers' instructions.[66] The Centers for Medicare & Medicaid Services (CMS) are responsible for implementation of CLIA, including laboratory registration, fee collection, surveys, surveyor guidelines and training, enforcement, approvals of PT providers, accrediting organisations and exempt states. The Centers for Disease Control and Prevention (CDC) are responsible for the CLIA studies, convening the Clinical Laboratory Improvement Amendments Committee (CLIAC) and providing scientific and technical support/consultation to DHHS/CMS. The Food and Drug Administration is responsible for test categorisation.

A number of professional bodies such as the CAP also play an important role that influences the overall provision of testing services in the USA. Reimbursement arrangements and clinician and laboratory staff norms are also important. As such, the system of oversight in the USA is viewed as being very complicated, even by those at the heart of it (CDC).

Under the CLIA legislation, laboratories that provide healthcare testing services must be CLIA-certified. However, these guidelines are regarded as setting a minimum standard only, due in part to the nature of the USA being a union of states and also the greater mix between systems of provision. As such, states are free to set their own rules and inspection regimes and some, such as New York and California, set stricter rules than others (CDC, lab 2). This means that laboratories in one state must abide by rules made by others, such as by the New York State legislature, if they are to test patients from that jurisdiction. As such they are inspected even though they may be practising thousands of miles away (lab 2). This particular aspect of the US framework for regulating diagnostics laboratories might be relevant for an EU framework, where differences in regulations exist between Member States.

If laboratories fail their proficiency test, that service can be removed from their CLIA certificate with no right to reimbursement from the CMS (lab 2), but this does not affect their other services (CDC). Physicians are not supposed to send samples to a laboratory without CLIA certification, but this does still occur, especially in the area of rare genetic disease testing where often a research laboratory is the only available location. In such circumstances legal proceedings could be initiated, but the CMS would generally play an educational role and work with the laboratory to bring its practice into compliance. Without a CLIA certificate, federal reimbursement from the CMS is not available for services, and this provides a strong incentive to maintain performance (lab 2).

"Many people have that misimpression…it's linked to the reimbursement process but it's not just linked to reimbursement, it is really linked to whether or not you can offer a service at all" (CDC respondent).

The major criticism levelled at the CLIA programme is related to the low frequency and lack of transparency of the inspections. Furthermore CLIA is not specific enough for full administration of genetic testing services and in May 2000 efforts began to develop a genetics specialty under the CLIA Act with the publication of a Notice of Intent for public comment. This elicited around 800 responses.

This process has been known to take 7 to 10 years (CDC). Meanwhile the CDC is actively engaged in other projects to shape the way in which genetic testing services are delivered. These include the ACCE project (recently finished) and its successor the EGAPP project. ACCE stands for Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social

66 Because problems in cytology laboratories were the impetus for CLIA, there are also specific cytology requirements.

implications, the aim being to build a methodology to help policymakers evaluate genetic tests prior to wide-scale introduction. The Evaluation of Genomic Applications in Practice and Prevention project is attempting to put into action the ACCE outputs together with previous advisory group recommendations and CDC findings to evaluate tests as they enter the clinic.

The role of clinical and research laboratories in developing new tests

Novel genetic tests are generally developed and used within the same institutions that provide services (CDC). This is viewed as part of the normal activities of the laboratories, as noted by one prominent pathologist in the College of American Pathologists newsletter: "Many molecular labs do translational research. They run studies that use data derived from other labs' specimens and add that to data from their own specimens to develop new tests that physicians can use. While appropriate scientific method is employed, labs do not apply the same rigour of CAP or CLIA guidelines to this translational research because it is not yet ready for prime time" (Daniel Farkas, 2003)[67].

Although not all laboratories engaged in PGx interviewed were molecular genetics labs, they were all developing their own assays for local use. Such "home brew" pharmacogenetic tests are provided by a wide range of commercial and not-for-profit laboratories. These include reference laboratories, often private, which provide a wide range of testing services, including for many rare conditions for clients over a wide geographic area, hospital-based clinical laboratories and university and hospital research laboratories. Yet very few PGx tests are being used in the USA at present (policy 2).[68] Activity in the area of metabolic testing seems to be low apart from Cytochrome P450 and TPMT testing (research labs 1 and 2, lab 2). Clinical demand for these tests remains low at present (lab 2). On the other hand, disease stratification testing is used more widely with around 60% of the 750-800 immunohistochemistry laboratories offering HER2 and Estrogen receptor testing (lab 4).

Although the FDA does require pre-market notification or approval for many types of in vitro diagnostics, specific reagents, including the active ingredient at the centre of a testing method, can be marketed without pre-market approval. However, there is a requirement for such reagents to be manufactured according to a Quality Systems Regulation (QSR) and for the laboratory to validate the performance of the assay in the population it intends to test. "Home brew" assays developed and used within an institution, a category that includes most genetic tests used in the USA, are not required to be submitted to the FDA, and face no federal regulation beyond CLIA certification (CDC [56]).

Because validation of new services is left up to the laboratory, this remains an area of concern at present. However, CLIA guidance on the development of new tests includes clear guidelines for validation, and guidelines published by a professional body, the Clinical Laboratory Standards Institute (CLSI) (formerly NCCLS), are often used by laboratories as a de facto standard for validation of new assays (lab 2, lab 3). This appears to be common practice, as the CLSI notes: "CLSI develops and publishes standards and guidelines through a unique consensus process involving government, professions and industry. All CLSI consensus documents are voluntary, but in certain instances, regulatory agencies or accrediting bodies will require that a specific CLSI standard or guideline be followed. Therefore, in order for an institution to meet the regulatory or accreditation

67 Quoted from "Keeping score: Daniel Farkas, PhD tracks the recent hits and misses in molecular testing"- Feature story, April 2003, CAP Today – available at www.cpa.org/apps/docs/cap_today.

68 Specific numbers of laboratories engaged in PGx testing are difficult to obtain, firstly because of uncertainties over the definition, and secondly because the online directory of genetic testing laboratories, www.genetests.org, does not contain any record of laboratories offering key PGx tests such as HER2, Cytochrome P450 and even terms such as "pharmacogenetic" yield no hits. Accessed on 16.4.2005.

requirements, following the standard or guideline becomes mandatory." (CLSI FAQs)[69]

Reimbursement – an indication of utility?

Although not a formal regulatory hurdle, the reimbursement of a test is evidence of some formal acceptance of its utility. Indeed it has been suggested that more could be done to raise the standard of laboratory testing by using reimbursement as a means to focus testing activity on more robust methods (lab 1). The reimbursement price is based on a decision by the CMS that sets the actual monetary value assigned to these tests, while not separately calculating each step (such as DNA extraction and PCR). Current reimbursement schemes for genetic testing methodologies have cleared the way for PGx tests also to be priced, although the relatively high content of manual processes in current tests means that pricing might be a more complex issue. Given the early stage of PGx, private healthcare reimbursement is made on a case-by-case basis, often at local level (lab 3). At this time, no national-level decisions have been taken by CMS regarding the reimbursement of PGx tests.

A central role for professional bodies

The College of American Pathologists is a privately run professional body with a central role in the oversight of PGx testing services – although it is not regarded strictly as a regulatory body (lab 4). Firstly the CAP has "deemed status" and can thus undertake CLIA certification inspections (see above). Secondly it runs its own CAP accreditation scheme. Finally, the CAP presides over a quality assurance review system known as Proficiency Testing (PT).

- The CAP accreditation scheme

CAP accreditation is viewed as more stringent than the minimum CLIA guidelines (lab 4). It is recognised by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which offers accreditation to a wide range of healthcare organisations rather than just laboratories),[70] and in a single accreditation process CAP-accredited laboratories can meet the full spectrum of standards necessary in order to service the broadest patient population.

- Personnel training

Under CAP accreditation regulations, pathology laboratory staff need to be trained as a pathologist or other specialised physician, or have a doctorate in a biological science, as well as having further specialised training or experience. Staff undertaking assays need to have extensive experience (4 years at least), as well as a suitable bachelors or masters degree. Technical staff also need to be qualified, although this can in theory simply take the form of experience of working with the director of the laboratory (CAP molecular pathology checklist, version 29.12.2004).

- Proficiency testing

The CAP manages a wide range of proficiency testing schemes in the USA.[71] These are run by advisory boards, including members with laboratory expertise in the specific area of proficiency being examined and often including members from other schemes to ensure a degree of cross-scheme learning and liaison (CDC, lab 4).

The only current PGx test with a proficiency test is the FISH HER2 test and this is not graded at present (lab 4).[72] The FISH HER2 scheme is run by

69 http://www.clsi.org/Template.cfm?Section=FAQ.
70 See http://www.jcaho.org/about+us/index.htm.
71 See http://www.cap.org/apps/docs/laboratory_accreditation/ptgraded.html updated November 2004.
72 See http://www.cap.org/apps/docs/laboratory_accreditation/ptgraded.html updated November 2004.

the Cytogenetics Resources Committee of the CAP. It was established after pilot studies in 1995 and 1996 and currently has around 150 laboratories participating in FISH testing [57]. There is pressure for the CAP to adopt more graded schemes, and users expect it to do so in the next couple of years (lab 4).

Where the CAP does not offer services, laboratories can organise ad-hoc proficiency testing programmes, by exchanging samples between themselves. This strategy is being actively explored by some groups working in pharmacogenetics where the CAP has not yet established a scheme, for example in areas like TPMT and Cytochrome P450 testing. However, interest is still relatively low (research scientist 2) and practice is very variable between laboratories, making comparative assessment difficult (lab 5).

These PT schemes have helped to secure agreement within a community of practitioners, and active collaboration between the committees involved in ICH and FISH testing for HER2, for example, has demonstrated the strengths and weaknesses of different technical approaches (see CAP 2002). Nonetheless even after several years of HER2 testing there are still disputes over methodologies and some laboratories are concerned about the continued use of immunohistochemistry methods, even using the commercial kit: "There's a lot of inter-observer variability, you know, it's really, it's a problem, but you know it is a general problem [in] immunohistochemistry I think… you can have everybody do a single test exactly the same way in every lab and still get result variability due to all these pre-analytic variables" (lab1).

At policy level, concern was expressed in the mid-1990s about the flexibility of the PT system; however, this does not appear to have been addressed since: "Current requirements under CLIA are inadequate to ensure the overall quality of genetic testing because they are not specifically designed for any genetic tests except cytogenetic tests. Most laboratories performing genetic tests voluntarily participate in quality programs addressed specifically to genetic tests, but they are not required to do so. Consequently, providers and consumers have no assurance that every laboratory performs adequately."[52]

Clinical use of PGx data

In the USA, legal responsibility for interpreting test results rightly lies with the physician, but very few physicians have digested information on PGx in a manner that allows them to use it pro-actively (lab 3). Therefore clinical laboratory staff have had to embrace the role of educators to the physicians, and ways to make this information available to physicians are increasingly a focus for discussion at professional meetings (lab 2, lab 3). At the same time, laboratory staff are discouraged from talking to patients as there is a danger that information can be misconstrued (lab 2). Certainly there is a problem in that physicians need to be trained in PGx, and sometimes know less than patients who have searched the web.

Multiple educational routes are expected to be necessary to achieve a level of physician awareness of PGx, with approaches such as direct mail, newsletters and web-based information all being pursued by some advanced centres to reach their clinical users (lab 2). The subject of how to inform test users better has become a focus in forums such as the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (lab 3).[73]

Some professional bodies are involved in providing discipline-based courses and workshops for continuing medical education, such as the American Psychiatric Association and the American Association for Clinical Chemistry. This may also be provided by commercial organisations. The National Coalition for Health Professional Education in Genetics, a cross-disciplinary professional body established in 1996,

73 See http://www.iatdmct.org/ accessed on 16.4.2005.

also organises conferences and training courses, some of which are focused on pharmacogenetics.[74] However, medical training in PGx is available at only a few medical schools, such as Harvard and the Mayo Clinic, and even then is limited by curriculum time pressures.

4.1.3 Remaining challenges for the regulation of PGx in the USA

A number of challenges have been identified by stakeholders relating to the regulation of PGx. Some of these have been mentioned in the previous sections, while the remaining challenges facing regulation of PGx are examined in more detail here.

The PMC has been actively highlighting the remaining challenges to be addressed, but it suggests that the technology raises few entirely new issues:

"None of theses issues is unique to personalised medicine; government regulation of clinical trials, intellectual property rights, licensing practices, healthcare reimbursement and privacy are areas that will need to be examined in the light of advances that are occurring in personalised medicine."[58]

Francis Collins at the National Human Genome Research Institute emphasises the need for clarity over the groups responsible for assessing the PGx tests as and when they become available for clinical use.[75]

The PMC suggests that there is a case for policy intervention and one of the main problems is obtaining sufficient policy support:

"The next generation of medical practice – personalised medicine – demands that policymakers adopt a coherent integrated approach to the legal, financial, social and professional issues that encircle this debate." (PMC [58])

Consequently, industry has been showing great interest in pharmacogenetics, and industry rather than government is likely to drive the spread of PGx testing in the USA (CDC). However, there is a feeling that commercial genetic testing in the USA in general is not adequately regulated and that some private laboratories could be offering PGx tests more widely than is advisable or than would be offered by not-for-profit laboratories (lab 2, policy 1).

The move into law of a genetics discrimination bill is still ongoing. This is seen as a key to strengthening legislation in the USA to support genetic testing more widely and is *"desperately needed"* (policy 2). However, there are only a small number of (albeit high-profile) cases linked with this issue at present (policy 1), and some laboratory staff suggest PGx testing does not raise as many controversial issues as other forms of genetic testing (lab 2).

Technical limitations still exist in that more cost-effective, more reliable, less complex tools are needed to generate data, both for clinical use and for research and development. Clinical laboratories are typically more financially restricted than those involved in industrial R&D, and as a result they often rely on SNP detection rather than expansive microarray analysis technologies.

Sufficient knowledge of genetic variability in the population is necessary for PGx tests to be robust in a clinical setting. This is often a problem, especially for genotyping as the characteristics of populations differ and there is currently an acute lack of data on genotype frequencies in many ethnic populations.

Translation from research into clinically useful information is also seen as a major challenge. Clearly there is a need for data on people with different genotypes and their responses to treatments and the relative effect of pharmacogenetic testing on clinical outcomes (research lab 1).[76]

74 See http://www.nchpeg.org accessed on 16.4.2005.
75 http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf.
76 See http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf.

Additional regulatory challenges (see section 4.1.1) have included the need to build up in-house know-how and form new ways of working, and the classification and validation of biomarkers. Stratification of populations in terms of drug use was not seen as a challenge, given the existing mechanisms for accelerated approval of "orphan" drugs. As such PGx appears unlikely to require further changes to the hurdles for drug approval.

There is a broad need to educate doctors and insurers on understanding and evaluating pharmacogenetic test results, as the current educational base for PGx is "very poor" (policy 2). The professional bodies should lead the way in educating doctors (research lab 2), and some of the leading institutions already offer training, although this is typically limited to 90 to 180 minutes of tuition. It has been suggested that the solution will be to train a new generation of doctors, but this could take a decade (lab 2) and therefore CME programmes are also needed.

As PGx testing is a newly emerging area, proficiency schemes have not yet been established for some tests, such as for Cytochrome P450 (research 1, lab 5). Even where schemes have been established, such as for tests like HER2 testing, there is concern that they do not have sufficient "teeth" (lab1) and are designated as educational schemes by the CAP. This means that the proficiency testing scheme does not grade laboratories participating in the scheme and they face no penalty for poor performance (lab 4).

Interpretation and clinical use of data requires an understanding of both genotypic and phenotypic factors. The field therefore crosses several disciplinary boundaries and these related activities need to be addressed by entities that cooperate and act in a coordinated manner.

Existing QA schemes vary in strength from field to field (lab 1), and the overall logistics of managing these schemes across the whole country is a challenge, especially to gain the depth of assistance for members that some European schemes are able to offer (lab 1, lab 4). To run the QA scheme, patient tissue or DNA samples are needed and these can be difficult to obtain in sufficient amounts, partly because of concerns by patients over the future use of these tissues (lab 2, policy 2). Once these have been obtained they need to be banked and cell lines established as sustainable sources for the QA scheme. This is costly and time-consuming (lab 2).

Overall, users seem satisfied with the current regulatory system for testing services, which is almost *"honour-based"*, respects their professionalism and allows innovation. They are anxious that any changes are undertaken carefully, especially where these could have an impact on the ability of laboratories to develop new "home brew" tests. In this respect rigid new requirements could be seen almost as an attack on the professionalism of laboratory staff (lab 3).

The low reimbursement level for genetic tests is seen as a problem delaying provision of such services by laboratories. This pricing system reflects the fact that medical testing in the USA is not really a market system – the reimbursement prices paid by insurance firms mirror those set by the CMS for Medicare. Medicare is by and large used by the elderly, and pricing does not necessarily reflect the market for PGx products.

A forthcoming report from the SACGT is expected to advise that reimbursement costs for genetic tests in general are too low and that there is therefore not a sufficient incentive to provide testing services for some rare genetic conditions (policy 2). However, there was some evidence that laboratories thought pricing levels are sufficient if the provider is testing at the appropriate volume to gain economies of scale (lab 3).

Changes to the CLIA system to incorporate genetic testing as a speciality are in the pipeline and would have some implications for some PGx tests.

Although limited tests are available for PGx in the USA at present, there is already one case of a laboratory which has ceased providing a service for TPMT genotyping due to a patent held by the biotech firm Prometheus. It is possible that patents

will make testing more expensive, although it may be too early to say.

4.2 EU frameworks for the regulation of PGx products

4.2.1 Drug regulation in the EU

European medicines regulation consists of a devolved system of assessment conducted by the national regulatory authorities of the 25 Member States, supported by a European-level expert advisory committee, the Committee for Medicinal Products for Human Use (CHMP), which prepares scientific opinions for the secretariat, the EMEA, and when necessary resolves disputes between Member States.[77]

Within this arrangement, there are two approval procedures, the **centralised procedure** and the **decentralised (or mutual recognition) procedure**. These harmonised procedures for the assessment of safety, efficacy and quality have been developed since 1965, and have been periodically reviewed and adjusted over this period. Only the basic features are outlined here, with an emphasis on recent legislative changes following review of existing arrangements and Community enlargement on the one hand and, on the other, growing recognition that newly emerging therapies and technologies such as pharmacogenetics could pose additional challenges for regulators.[78]

Applications for marketing authorisation (MA) for biotechnology products must go through the centralised procedure. Since November 2005 the centralised procedure has been mandatory for products for oncology, diabetes, HIV and genital diseases. The centralised procedure results in a Europe-wide MA. Under the procedure, the EMEA appoints two Member States to be responsible for assessment (rapporteur and co-rapporteur). The Committee for Medicinal Products for Human Use (CHMP) reviews the assessment report and decides on authorisation.[79] If the CHMP recommendation is positive, MA is then formally granted by the European Commission in the form of a Decision.

The decentralised (mutual recognition) procedure allows sponsors to apply for MA in one Member State (known as the "reference Member State") and, if approved, to request mutual recognition of that national authorisation by other Member States ("concerned Member States"). If a concerned Member State disagrees with the original assessment, the CHMP reviews the application and makes a recommendation that is binding on all parties.

These procedures are founded on a legal framework comprising a series of Community Directives and Regulations adopted since 1965, with the dual aims of improving patient care and achieving a single EU-wide market for pharmaceuticals. Creation of a single market is viewed as providing patient benefits and enhancing the quality of life of European citizens while also strengthening the competitiveness and research base of the European pharmaceutical industry (European Commission 2000).

The first Directive (Directive 65/65/EEC) introduced a system of compulsory authorisation for all Member States. A decade later, two further landmark Directives (Directives 75/318/EEC and 75/319/EEC) introduced a system of

77 A network of European experts underpins the scientific work of the EMEA and the CHMP. For more on the EMEA and CHMP see: http://www.emea.eu.int. Note also that although there has been a series of name changes original acronyms have been retained – the EMEA is now the European Medicines Agency but retains the abbreviation EMEA, and the Committee for Medicinal Products for Human Use is the CHMP, formerly the CPMP (Committee on Proprietary Medicinal Products). The term CHMP is used throughout to refer to the CHMP or CPMP.

78 Note that the EMEA refers to "emerging therapies and technologies", including PGx (http://www.emea.eu.int/htms/human/itf/itflinks.htm) whereas the Commission uses the term "advanced therapies" to refer to gene and cell therapies and tissue engineering, but not PGx.

79 In practice the process is, of course, more complicated than this and is invariably an iterative one, with a list of questions prepared by the Committee to be answered by the sponsor before the Committee arrives at a final decision. Also, recommendations are often subject to the MA holder undertaking additional work, to clarify therapeutic action or clinical utility, possible side-effects or other issues.

mutual recognition of national MA by Member States. To facilitate mutual recognition, the latter Directive established the Committee for Proprietary Medicinal Products (CPMP) – now replaced by the Committee for Human Medicinal Products (CHMP) – to assess whether products complied with 65/65/EEC and to resolve disputes through binding arbitration.[80] Together, these three Directives laid the foundations for a Europe-wide system of harmonised medicines regulation and a single Community-wide market in pharmaceuticals [59].

Implementation of mutual recognition was slow, and in 1995 a new structure was introduced[81] setting maximum time limits for assessment and reducing the grounds for objection by Member States. It also provided two routes for authorising medicinal products: a new centralised procedure with applications made direct to a new Agency[82] – known since April 2004 as the European Medicines Agency (although the acronym "EMEA" remains) – and a revised "mutual recognition" or "decentralised" procedure applicable to most conventional medicinal products.[83]

Applications under the decentralised procedure are made to those Member States where the applicant chooses to market the product, and the procedure operates by mutual recognition of the original MA.[84] Disputes between Member States are resolved through binding arbitration by the CHMP. Since establishment of the decentralised procedure, a Mutual Recognition Facilitation Group (MRFG)[85] has also been set up by Member States to help resolve problems between states, and to coordinate and facilitate the procedure.[86]

Some ten years after its establishment, the European regulatory framework is undergoing another round of changes, although the two approval routes outlined above remain broadly the same.[87] The principal new legislation comprises Regulation (EC) No 726/2004[88] and Directive 2004/27/EC[89] which amends Directive 2001/83/EC on the Community code relating to medicinal products for human use.[90]

Regulation (EC) No 726/2004 also extends the scope of the centralised procedure by making the procedure mandatory, with effect

80 Subsequent problems with implementing these Directives were examined by the European Commission's Pharmaceutical Committee, set up by Directive 75/320/EEC.

81 Full, definitive information on the Rules Governing Medicinal Products in the European Union is available at the DG Enterprise website at: http://pharmacos.eudra.org/F2/eudralex/index.htm.

82 Prior to the creation of the EMEA, biotech and other innovative products were submitted to a "concertation procedure" – see Abraham, J. and Lewis, G. (2000) Regulating Medicines in Europe: Competition, Expertise and Public Health, Routledge, London.

83 Council Regulation (EEC) No 2309/936 and Directive 93/41/EEC.

84 Applications are made to one Member State (reference Member State) which assesses the application and decides whether to approve it or not, and this decision is then recognised by the other Member States where approval is sought (concerned Member States). National authorisations are available for medicinal products to be marketed in one Member State only.

85 The MRFG was established by the Member States in 1995. Originally an informal initiative, the arrangement has now been formalised in legislative terms. The MRFG meets monthly at the same time as the CHMP and comprises representatives from each Member State, chaired by the country which holds the Presidency of the European Union. For more details see the Heads of Agencies site at http://heads.medagencies.org/ (Accessed 15/05/05).

86 For more details on current European procedures see the EMEA site at www.emea.eu.int and European Commission (2000). For an analysis of the development of European medicines harmonisation and establishment of the EMEA, see Abrahams and Lewis (2000) "Regulating Medicines in Europe: Competition, Expertise and Public Health", Routledge, London.

87 EMEA (2005) "EMEA Implementation of the New EU Pharmaceutical Legislation", available online at: http://www.emea.eu.int/htms/general/direct/legislation/background.htm, accessed on 25.5.2005. European Commission (2005) "European Commission Review of Pharmaceutical Legislation", available at: http://pharmacos.eudra.org/F2/review/index.htm, accessed on 23.5.2005.

88 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

89 Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

90 Latest legislative changes are available at the EMEA website: www.emea.eu.int and at the European Commission, DG Enterprise and Industry site: http://pharmacos.eudra.org/F2/review/index.htm.

from 20 November 2005, for orphan medicinal products and for products to treat acquired immune deficiency syndrome (AIDS), cancer, neurodegenerative disorder or diabetes. With effect from May 2008, the centralised procedure will also be mandatory for medicinal products for human use containing an entirely new active substance and for treatment of auto-immune diseases and other immune dysfunctions and viral diseases.[91]

4.2.2 Regulation of in-vitro diagnostics

Turning to the EU regulatory framework for in vitro diagnostics, as noted already, competence for medical devices resides with Member States, with the primary legislation applicable to in vitro diagnostics at European level being the **IVD Directive** (Directive 98/79/EC).[92] The IVD Directive, which was published in December 1998, introduced a transitional process aimed at harmonising minimum requirements for devices across Europe, and scheduled to commence 18 months after its publication.[93]

The Directive introduced the first common regulatory requirements dealing specifically with the safety, quality and performance of in vitro diagnostic medical devices, thereby bringing them into line with other medical devices. The Directive is intended to ensure that in vitro diagnostic medical devices do not compromise the health and safety of patients, users and third parties and attain the performance levels attributed to them by their manufacturer.

The relevant provisions of the Directive came into force in June 2000. Following the transitional period, from December 2003 in vitro diagnostic medical devices placed on the market have to comply with the Directive and associated Regulations. Non-compliant in vitro diagnostic medical devices placed on the market by this date had to be put into service (i.e. first made available to a final user) by December 2005. In vitro diagnostic medical devices which are put into service but not placed on the market had until December 2005 to comply with the legislation. This arrangement meant that, during the five-year transition period, both CE-marked and non CE-marked in vitro diagnostic medical devices could be placed on the EU market, and manufacturers were allowed to choose whether to follow the Directive or national requirements. Since December 2003, only CE-marked devices have been allowed onto the market and from December 2005 only CE-marked devices can be "put into service".[94]

The Directive defines an in vitro diagnostic medical device as:

"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information: concerning a physiological or pathological state, or concerning a congenital

91 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. The CHMP released a Consultation Paper on how to define these areas in June 2005, based on the International Classification of Diseases (version 10) (CHMP 2005).

92 The In Vitro Diagnostic Medical Devices Directive (98/79/EC) was formally adopted in October 1998 and published in the Official Journal of the European Communities on 7 December 1998 (OJ No L 331, 7.12.1998, p.1).

93 Directive 98/79/EC was published in December 1998. See Official Journal of the European Communities L 331. The Directive provided for a 12-month period for transposition into national law, i.e. until 7 December 1999.

94 "Putting into service" is defined as "The stage at which a device has been made available to the final user as being ready for use on the Community market for the first time, for its intended purpose".

abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures".[95, 96]

This definition makes it clear that an in vitro diagnostic medical device in the form of a pharmacogenetic test is covered by the Directive. According to the Directive, the conformity assessment procedures also apply to the manufacture of in vitro diagnostic medical devices not placed on the market but put into service and used within the context of professional activity (see Article 9(13) of the Directive) (MHRA n/d).

Consequently, the provision of diagnostic services, such as "home brews" would generally also need to comply with the appropriate conformity assessment procedure for that device.

The purpose of the IVD Directive is to supplement the Community legal framework governing the conditions for the marketing of medical devices by extending legislation to include in vitro diagnostics. To ensure uniform Community rules, it has been broadly based on Directives 90/385/EEC (active implantable medical devices) and Directive 93/42/EEC (medical devices). In-vitro diagnostic medical devices constitute a sub-category of the medical devices defined in Directive 93/42/EEC which consists of devices used in medicine for the in vitro analysis of human bodily specimens.

Medical applications include analyses to assess a person's health (e.g. cholesterol, pregnancy testing), to check for disease or congenital abnormality, to monitor treatment as it proceeds (for instance, dose and effect of medicinal products) or to determine the safety and compatibility of donated organs or blood (e.g. testing for HIV or the hepatitis virus). The Directive lays down the essential requirements as regards reliability of the devices, suitability for the intended purpose, and protection of users and third parties. In addition, it harmonises the conformity assessment procedures before the manufacturers may place devices on the market.

While the IVD Directive generally follows the approach of the general Medical Devices Directive (Directive 93/42/EEC), it adds some important developments. These include a list of in vitro diagnostic medical devices regarded as sensitive (Annex II to the Directive), and specific provisions for the most sensitive products on market surveillance, and on the introduction of particular health monitoring measures and rules applicable to the "notified bodies".

For a whole range of in vitro diagnostic medical devices, with the exception of self-test devices, Article 9, in conjunction with Annex III, of the Directive provides for checking the design and the manufacturer's responsibility without the intervention of a third party (i.e. a notified body). This reflects the fact that the great majority of devices covered by the Directive involve no direct risk for the patient and, with the exception of "self-test" devices, are used primarily by properly trained professionals. Furthermore, the results of the analyses may often be confirmed by other means. However, in the case of a number of sensitive devices such as those specified in lists A and B in Annex II to the Directive, the intervention of a notified body is needed before a device can be placed on the market. These are specific devices where accuracy is essential for medical

95 MHRA (n/d) Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC available at: http://www.mhra.gov.uk/mda/mdawebsitev2.nsf/72a26a46ed28515400256a7600410653/0a5e025f3bac561180256bf100387fd3/$FILE/direct19.pdf (accessed on 21.6.2005).

96 According to the UK MHRA guidance on the IVD Directive, this definition needs to be read in conjunction with the definition of a medical device, which states that "a 'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (MHRA (n/d) 'Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC', available at: http://www.mhra.gov.uk/mda/mdawebsitev2.nsf/72a26a46ed28515400256a7600410653/0a5e025f3bac561180256bf100387fd3/$FILE/direct19.pdf (accessed on 21.6.2005).

practice and any malfunction is likely seriously to endanger health.[97, 98]

4.2.3 Clinical Trials Directive

The other notable development relevant to PGx development in the EU is the **Clinical Trials Directive** (2001/20/EC)[99] which introduced additional responsibilities for regulatory authorities, for ethics committees, and for anyone running or supporting clinical trials of medicinal products. The scope of the Directive, published in May 2001, is wide, covering the conduct of all clinical trials (CTs) in the EU involving medicinal products, as defined in Article 1 of Directive 65/65/EEC. In practice, every clinical trial involving medicinal products is covered, whether sponsored by industry, government, research councils, charity or a university.

The Directive sets standards for protecting clinical trial subjects, including incapacitated adults and minors. Importantly, it will also establish ethics committees on a legal basis and provide legal status for certain procedures, such as times within which an opinion must be given. It also lays down standards for the manufacture, import and labelling of investigational medicinal products (IMPs) and provides for QA of clinical trials and IMPs. To ensure compliance with these standards, it requires Member States to set up inspection systems for Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). It also provides for safety monitoring of patients in trials and sets out procedures for reporting and recording adverse drug reactions and events. To help exchange information between Member States, secure networks will be established linked to European databases for information about approved clinical trials and pharmacovigilance. The rules in the Directive do not distinguish between commercial and non-commercial clinical trials.

Overall, the Directive provides for significant new controls which will affect clinical research and development of medicinal products in Member States, with specific timescales for ethics review, a requirement for approval of phase I clinical pharmacology studies on healthy volunteers, manufacture of IMPs only at licensed manufacturing sites under GMP conditions, and introduction of inspections to assess compliance with GMP and GCP at sites which are involved in clinical trials of medicinal products (industry, hospitals, universities and other places).

One concern expressed has been whether introduction of the Clinical Trials Directive will impede the conduct of trials, in particular by academic researchers, although this remains an open question.[100]

If such criticism proves valid, it is possible that incorporation of academic research into broader PGx development could be hampered to some extent by the demands of the Directive, although whether this will be the case is currently an open question.

4.2.4 Pharmacogenetics and the EMEA

In the context of PGx and the European regulatory framework, the EMEA expects industry to use both centralised and decentralised routes for approval. However, the extent to which these

97 MHRA (n/d) Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC available at: mhra.gov.uk/mda/mdawebsitev2.nsf/72a26a46ed28515400256a7600410653/0a5e025f3bac561180256bf100387fd3/$FILE/direct19.pdf (accessed on 21.6.2005).

98 List A contains devices such as reagents and reagent products for the determination of blood groups and for products used in the context of blood transfusion and the prevention of AIDS and certain strains of hepatitis. List B contains devices such as reagents and reagent products for the determination of irregular anti-erythrocytic antibodies and of certain human infections.

99 Full title: Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials. Text available at http://www.europa.eu.int/eur-lex/en/search/search_lif.html.

100 For example, the UK Academy of Medicine has criticised some of the demands in the Directive, including what it describes as "the onerous legal and administrative responsibilities imposed on the trial 'sponsor'". Research Fortnight (2003) "View from the Top: Small innovative clinical trials are under threat: One size of regulation does not fit all when it comes to clinical trials, says Patric Vallance" (4 May).

routes are utilised in practice is likely to be shaped by two factors: the extension of mandatory submission requirements for certain therapeutic areas,[101] and the fact that the proportion of products submitted to the centralised procedure is increasing and this trend is expected to continue.[102]

4.2.4.1 Building scientific capacity at the EMEA

One key question is whether regulatory agencies have sufficient expertise in technical and social issues relating to PGx. The growing interest in the use of PGx techniques in drug development and the promise of targeted treatment has led a number of authorities, including the FDA and EMEA, to build up their scientific capacity in this area by appointing additional experts recruited from academia. Other examples include the Chinese (with particular interest in PGx and traditional medicines), Taiwanese, and South Korean agencies.

The EMEA has also established the CHMP PGWP composed of experts in assessment of the safety, efficacy and quality of medicinal products. The PGWP also has direct input from academic members.[103] The PGWP is supported by specialists in different therapeutic domains who provide expert advice. At the time of the interview, the availability of expertise was being re-examined, with the expectation that capacity would be extended further, particularly with regard to the evaluation of PGx testing methods used in MAAs.

The Agency has made efforts to consult both industry representatives and other government bodies at European level. In 2004 EMEA specialists held the first of several planned meetings aimed at bringing together the network of interests from different EU bodies (European Commission, DG for Research and DG for Enterprise) and industry. In 2000 EMEA identified a series of needs that were addressed over the following four years. Developments included: establishment of a PGx Expert Group, which was replaced by the PGWP in May 2005,[104] publication of the EMEA Working Paper on Terminology, and a number of international activities. A second workshop was held in late 2004.[105] Outputs from some of the activities relating to emerging technologies, including PGx, are publicly available on the EMEA website.[106] The EMEA has also published a Discussion Paper on a proposed Road Map for the future of the Agency.[107] According to the EMEA, the Road Map has some points in common with the FDA's Critical Path Initiative,[108] which concerns faster development of safe and efficacious new drugs through the development of new assessment methods and procedures.[109]

The most important challenges facing the EMEA with regard to PGx development are similar to those the Agency faces with other new science applications with respect to pharmaceuticals, although different in both quantity and, in some

101 EMEA (2005) Committee for Medicinal Products for Human Use (CHMP). Guideline on therapeutic areas within the mandatory scope of the centralised procedure for the evaluation of marketing authorisation applications with reference to Article 3 and Annex of Regulation (EC) No 726/2004. Draft. EMEA/180921/2005 (1 June).

102 The addition, from November 2005, of specific indications to the list of products that must go through the centralised procedure can be expected to increase this trend.

103 These individuals are leading academics from departments of genetics or possess special expertise in the field (EMEA respondent).

104 For details of PGWP membership see: http://www.emea.eu.int/htms/general/contacts/CHMP.html. The PGWP is chaired by Dr Abadie, Vice-President of the Scientific Committee, and the deputy chair is Prof. Flamiaon, both of whom are CHMP members.

105 The EMEA will probably publish the Proceedings of the Workshop, but had not done so at the time of writing.

106 http://www.emea.eu.int/htms/human/itf/itfintro.htm (accessed 22/06/05).

107 EMEA (2004a) "Discussion Paper, The European Medicine Agency Road Map to 2010: Preparing the Ground for the Future, Executive Summary", 23 March. Available at: http://www.emea.eu.int/pdfs/general/direct/directory/3416303en.pdf (Accessed on 25.5.2005); EMEA (2005) "EMEA Implementation of the New EU Pharmaceutical Legislation", available at: http://www.emea.eu.int/htms/general/direct/legislation/background.htm (accessed on 25.5.2005).

108 FDA (2004) "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products", US DHHS, Food and Drug Administration (March).

109 An overview of the Road Map is available at: http://www.emea.eu.int/htms/general/direct/roadmap/roadmapintro.htm

senses, nature. In the opinion of one source, from a knowledge management point of view, PGx is no different to other technologies, but it does raise some specific social and ethical issues.

The relationship between a drug and a diagnostic is potentially challenging in the European context as compared with the US market, because of the separation of legislative frameworks for the two product types and, therefore, the separation of assessment responsibilities between the EMEA and Member States, although this is not the view of the EMEA (see for example [10, 53]).

Potential scientific and regulatory challenges associated with the co-development of drugs and diagnostics were highlighted by the FDA in its recently published Concept Paper on the subject.[110]

The EMEA has been supporting PGx development since 2002 with establishment of a dedicated expert group on PGx – the first by any authority. These activities were not user fee-based, but were supported by core funding.[111] According to its spokesperson, the EMEA invests in expertise for coping with emerging technologies which appear likely to affect the development of future medicines. EMEA believes the potential impact on public health is huge, with major change likely "in the way drugs are developed, and in the way pipelines and strategic choices will be drifting in the next 20 years." However, the changes will not be revolutionary but rather a steady evolution. Meanwhile, the EMEA sees dissemination of PGx information as a key objective and route for facilitating further progress on PGx (EMEA respondent).

With regard to PGx, at this stage it is difficult to predict what and where the greatest impact will be although some experts suggest that in the first stage the main impact would be improved drug safety. Improving drug efficacy could take longer. Nonetheless, the EMEA believes the potential impact on public health is huge, with major changes in drug development likely "in the next 20 years." These changes "will creep in gently, and they have already started creeping in" (EMEA respondent).

Although the science of PGx has been progressing rapidly, with many publications, the impact on drug development has not been significant until relatively recently. The EMEA's devolved model of operation meant that this commitment to PGx education has itself presented problems because the Agency has needed to reach out to assessors in each of the Member States and in each area (quality, efficacy and safety). To expedite the task of managing and disseminating this knowledge, the EMEA has appointed senior assessors from the respective Working Parties for each of these areas to the Expert Group on PGx. These individuals also serve as liaison officers, informing the Working Parties in turn about developments within the working party. The potential logistical challenges posed by knowledge management and the need to acquire and disseminate information arise in part because the PGWG is based on scientific expertise and not representation, in contrast to EMEA Working Parties.

The development of EMEA guidance documents is a key part of the education process, serving the purposes of both industry and regulators. However, the primary purpose of such documents is "to establish criteria which have to be used by industry for preparing files and by our assessors to ensure that the established criteria are adhered to" (EMEA respondent).

4.2.4.2 EMEA briefing meetings

Another important development was the introduction of briefing meetings in 2002. These are meetings with individual sponsors outside the

110 FDA (2005) "Drug-Diagnostic Co-development Concept Paper – Preliminary Draft", DHHS, FDA, April. Available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed on 25.4.2005.

111 Similar moves have been made with regard to gene therapy and tissue engineering and now in the area of nanotechnology. The EMEA has had a Gene Therapy Expert Group since 1999.

formal regulatory decision-making process and, in the case of PGx data, roughly equivalent to the FDA voluntary genomic data submission scheme (VGDS). However, the remit of briefing meetings is broader and not restricted to PGx. To date, some ten companies, often with a different focus, some on the development of diagnostic tests rather than drug development, others on both, have requested such meetings across a range of therapeutic areas.

Differences in approval structures for medicines and diagnostics are perceived as a possible barrier to PGx development in Europe. As described above, therapeutic agents are approved either through the centralised procedure or by mutual recognition via the decentralised procedure. Both procedures are essentially European routes to approval, with a European scientific advisory committee, the CHMP, playing a central role in authorisation decisions either directly in the former case or by providing binding decisions if disputes arise in the decentralised procedure.[112]

The EMEA believes that enactment of the IVD Directive presents an opportunity for developing a fair and equal approach to diagnostic approval across Europe rather than presenting additional barriers to development. However, validation and certification of diagnostic products (i.e. analytical validation and CE marking) resides with national authorities and there is no requirement for demonstration of clinical utility in the European context. The lack of a requirement to demonstrate clinical utility may therefore need to be addressed in the context of PGx because clinical utility is a key factor in clinical uptake [10].

For these reasons, it is possible that the subject may need to be re-visited by the Commission in order to ensure that in cases where it is stipulated that a drug is to be used with a very specific test, the required information is attached in a clear and coherent manner.

The EMEA is not legally empowered to co-approve drugs and PGx tests. As the EMEA emphasised, the Agency does not examine diagnostic tests and neither seeks to do so nor envisages doing so in the future. If the need were to arise the Agency would go to the Commission to discuss the issue, but at present it has had no need to do so.

The formal channel of communication between the national diagnostics authorities and the EMEA is likely to become an issue. Even the genomic tests for the anti-cancer agents Herceptin and Erbitux are currently intended for diagnosis, and not as a part of a package or kit comprising both drug and diagnostic. In the EMEA's view, the trend is towards a situation where the diagnostic becomes a more sophisticated method for describing an indication for a drug. For example, in the case of the recently approved product, Erbitux, it is "strongly recommended" in the SPC (Summary of Product Characteristics) that the test be used before treatment in order to identify the patients in which it is likely to be efficacious. The EMEA's powers extend only to the labelling in such cases and not to mandatory use of a test or approval of the drug and diagnostic as a single unit or "package".

As the EMEA spokesperson put it: "The fact that a test can identify a polymorphism or a metabolising enzyme does not imply that you have to use this test for all drugs that go through that metabolising enzyme in order to use the drug in a certain way."

However, the conditions attached to use of a test and how such conditions or recommendations are disseminated or enforced (and indeed, whether they should be) is a global issue in the context of PGx and it has been suggested this may require further consideration by all regulatory agencies [53].

Under current legislation the situation becomes much more complex if the test is used

112 In the case of the decentralised procedure, the Mutual Recognition Facilitation Group (MRFG), which comprises representatives from all Member States' regulatory authorities, also plays a key role in settling differences.

in a patient with a given genetic feature or marker. Marketing authorisation for a test linked to a product that segmented patients (i.e. rather than segmenting a disease) would be considered only if a significant difference in risk/benefit was demonstrated, and where this difference could not be addressed in any other manner (such as by dose adjustment). As our EMEA respondent told us: "Of course, we are not going to add burden to the physician, to the patient, to society, for something that can be addressed without this additional burden. [Leaving to one side the issue of cost effectiveness] in terms of clinical utility, if there is no real difference in using the test or not using the test, and there is no simple way to address any small difference you might have, then of course we have to go for [the] compulsory test. But we have not yet been confronted with that" (EMEA respondent).

Whilst there is no single authorisation for diagnostics in the EU, the EMEA would value collaboration with national authorities in order to evaluate the clinical utility of a PGx test where this has a direct impact on the safe and efficacious use of a drug. However, approval of a given test for a given drug is potentially problematic, especially if the products are manufactured by separate firms and the companies disagree over the product's characteristics. As noted already, the Agency expects both centralised and decentralised procedures to be used to obtain marketing authorisation for PGx products, including their safe and efficacious use with a mandatory diagnostic test.

In the European system, the approval route chosen is a decision for the sponsor. There is always freedom of choice, except for the therapeutic areas where it has become mandatory to use the centralised procedure since November 2005 (oncology, diabetes, HIV and genital diseases) which, it should be noted, are areas where PGx is more advanced.[113]

With regard to whether the existing regulatory framework encourages PGx development, although formal decisions have yet to be taken, there is a belief that some changes will be required to the existing rules and regulations. For example, Commission staff have commented informally that the word "pharmacogenetics" does not appear in any of the current regulatory documents which form the basis for submission. The Common Technical Document (CTD) does not explain which data should be included in relation to a PGx test, for example, or detail where in the document this should appear. Nor does it say how a test should be evaluated if it is not a commercial kit but a lab-developed or "home brew" test, or where this information should be placed within the regulatory submission.

Nonetheless, the EMEA, in consultation with the Commission, has identified a number of areas that require attention. With regard to data submission for briefing meetings, in 2005 the CHMP made minor changes to clarify arrangements.[114]

The Agency also recently released the following guidance documents on PGx (http://www.emea.eu.int/htms/human/itf/itfguide.htm February 2006):

- Guideline on Pharmacogenetics Briefing Meeting (released for external consultation on 17 March 2005) EMEA/CHMP/20227/04 based on a 2003 Concept Paper on the subject, Concept Paper on Pharmacogenetics "Briefing Meetings" EMEA/CPMP/4445/03.

113 Note that the type of products required to be submitted via the centralised procedure for "public health reasons" will be extended from 2008 to include therapeutic areas such as auto-immune diseases. Note also that because the criterion used for optional submission is "scientific, technical and therapeutic innovation" it will be possible to submit generic, and even OTC, products via the centralised procedure from 2008 if they meet these criteria.

114 CHMP (2005) Committee for Medicinal Products for Human Use (CHMP). Draft Guideline on therapeutic areas within the mandatory scope of the centralised procedure for the evaluation for marketing authorisation applications with reference to Article 3 and the Annex of Regulation (EC) No 726/2004. EMEA/180921/2005 London, 1 June.

- A Concept Paper on the Development of a Guideline on Biobanks Issues Relevant to Pharmacogenetics (Released for external consultation in March 2005) EMEA/CHMP/6806/05.
- Details of the Mandate, Objectives and Rules of Procedure for the CHMP Pharmacogenetics Working Party. EMEA/CHMP/101592/04
- Understanding the terminology used in pharmacogenetics [REF: Understanding the terminology used in pharmacogenetics, EMEA/3842/04] – an update of an earlier paper on terminology [REF: EMEA/CPMP/3070/01 Position Paper on Terminology in PharmacoGenetics] a subject that is clearly essential for discussion of regulatory issues and improved understanding across Member States and internationally.

As well as establishing the Innovation Task Force, the Agency has also sought to clarify the purpose and structure of briefing meetings. Briefing meetings are designed to provide: an informal forum for discussion between individual applicants and regulators early and ahead of any future regulatory procedure, e.g. orphan drug designation, scientific advice or submission of a marketing authorisation application.[115]

The scope of the briefing meetings covers regulatory, scientific and other issues arising from the development of new therapies and technologies. Any information submitted for discussion is kept confidential, and additional EU scientific experts may participate in discussions as appropriate.[116]

According to the Agency: "Briefing meetings may also be the first step for regulatory classification of those medicinal products for which confirmation is needed with regard to their status and the applicability of pharmaceutical legal provisions before access to EMEA scientific advice, orphan medicinal product designation and marketing authorisation procedures is possible."[117]

With regard to voluntary submission of data via a briefing meeting, one difference between the US and European situations is that the FDA has defined different categories of biomarker and related legal ramifications relating to an IND (Investigational New Drug) and NDA (New Drug Application).

The briefing sessions are not procedures at national level but are informal meetings at European level with a selected group of expert members of the PGWP.[118]

To date about ten briefing meetings have been held, and about fifteen case studies with real products in development have been discussed informally at such meetings.[119] A new development is that the EMEA and FDA now hold joint briefing meetings with sponsors when requested to do so.[120] In this context, cooperation between EMEA and FDA has been recently intensified with the extension of a confidentiality agreement which includes a focus on pharmacogenomics and will allow exhange of information on legal and regulatory issues, scientific advice, inspection reports, marketing authorisation procedures and post-marketing surveillance.[121]

4.2.4.3 PGx data and marketed products

One crucial area of possible concern that was highlighted relates to the availability of research results and experience from within academia with regard to genetic determinants applicable

115 http://www.emea.eu.int/htms/human/itf/itfintro.htm (Accessed on 16.5.2005).
116 http://www.emea.eu.int/htms/human/itf/itfintro.htm (Accessed on 16.5.2005).
117 EMEA (n/d) "Emerging Therapies and Technologies", available at http://www.emea.eu.int/htms/human/itf/itfsupport.htm (accessed on 16.5.2005).
118 Briefing meetings are informal meetings in that they are not part of the formal process of obtaining MA for a product.
119 Reportedly one case was discontinued, but this product was later discovered to be identical to another one being developed.
120 FDA (2004) "Confidentiality arrangements concluded between the EU (EC and EMEA) and the US FDA/DHHS. Implementation Plan for Medicinal Products for Human Use". Finalised. 16 September 2004.
121 Cooperation on medicines regulation intensified: The EU-FDA confidentiality arrangement reviewed, 13 March 2006 http://www.emea.eu.int/pdfs/general/direct/pr/9309006en.pdf

to existing products, and how this experience might have an impact on, and be incorporated in, regulatory decision-making to improve use of such drugs.

There are no incentives to introduce information related to genetic determinants of the safety and efficacy of existing drugs. While there might be a case for incentives it is not within the remit of the EMEA to suggest such action. The EMEA does not have primary competence in this area and can only influence national authorities.

Under current arrangements, it may be possible to introduce changes to existing labelling via "Article 31 legislation", which allows Member States to request changes to the SPC and labelling of approved products if new data become available. This legislation could apply to new PGx data that become available, should a Member State wish to invoke Article 31 for public health reasons in such circumstances.

In the USA, the FDA is on record as expecting to re-review marketed products with a view to possible re-labelling if application of PGx techniques, such as patient genotyping prior to treatment, leads to documented improvements in efficacy or reduces serious toxicity.

One example where this has already occurred in the USA is the anti-cancer agent, irinotecan (Camptosar, Pfizer) which was relabelled to reflect PGx information collected following approval.[122] Some patients treated with the drug suffer severe and prolonged neutropenia and the incidence of this adverse effect has a strong genetic component. The drug is available in Europe and was registered through the decentralised system (see below). Recent work has shown that a genetic variant of an enzyme involved in the metabolism of the drug is associated with a very significant increase in the risk of neutropenia.[123]

In the USA irinotecan was relabelled as a result of significant additional work by the manufacturer, Pfizer, with the FDA Advisory Committee strongly recommending use of the relevant test in order to minimise the risk of neutropenia. The EMEA is in contact with FDA colleagues on this topic, but at the time of writing no decision had been taken with regard to similar action in Europe. The expectation is that information received from the FDA will be distributed to Member States in order to allow them to decide what, if any, action to take with regard to labelling requirements for the drug.

Irinotecan could be the first example where a PGx test is the most powerful tool to reduce significantly a major toxicity problem with a previously approved drug that cannot be prevented by reducing the dose or by other means. Another possible example where relabelling could occur in the future is the widely used anti-coagulant drug, warfarin, where the FDA has said it will review the existing label and recommendations for use if current studies show outcomes are improved through prior genotyping of patients.[124]

4.2.4.4 Submission of PGx data as part of a marketing authorisation application

One issue likely to face regulatory authorities is the extent to which they will, or should, demand PGx data in submissions. In the case of the EMEA, there has been limited discussion within the Agency on the circumstances, if any, in which compulsory submission of PGx data would be considered helpful or demanded. The Agency's view is that such demands are effectively restricted to voluntary submission via briefing meetings because of the legal status of a Marketing Authorisation Application (MAA). Products seeking MA arrive at the EMEA as fully

122 FDA (2005c). "Letter to Pfizer Inc. dated 7 June 2005. [with regard to supplemental new drug application dated March 30, 2005, received on 1 April 2005, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for CAMPTOSAR® (irinotecan hydrochloride injection), 20 mg/ml.]", available at: http://www.fda.gov/cder/foi/appletter/2005/020571s026ltr.pdf. (Accessed on 22.6.2005).

123 Another less severe side-effect of the drug is diarrhoea.

124 Current PGx studies on warfarin include a major prospective study involving 2400 secondary and primary care patients in the UK http://www.genres.org.uk/prp/projectsliverpool2

developed products complete with clinical data. In such circumstances it is difficult to envisage demanding additional information unless there is specific evidence of adverse events or lack of efficacy for a sub-population of patients. Therefore it is unlikely for the time being that the Agency would ask for PGx studies to be conducted on a submitted MAA. However, it is conceivable that a company could be advised to undertake PGx studies during the scientific advice process in order to facilitate eventual approval.

4.2.4.5 Labelling of PGx products

As mentioned earlier, the EMEA expects PGx technology to impose changes to the legal framework, such as the format of data in the MAA. Labelling of a PGx product and its related diagnostic test would also require attention. At present there is no requirement to include information on the diagnostic component on the drug label in an organised fashion. In the case of Erbitux, for example, information on the test is available, but in a number of different places on the label.[125] In addition, at present there is no method that allows the EMEA to update label information. The possibility of updating the label with information that becomes available post-marketing is a key avenue for introducing PGx, as exemplified by the recent re-labelling of irinotecan in the USA. How such information is positioned on the label will also require clarification.

In many cases, PGx tests are likely to be provided by commercial laboratories, and provision of these services may also require attention, with the creation of Europe-wide standards for QA to guarantee the quality and accuracy of all genetics-related testing across the Community. However, it is not clear how this might be carried out or how standards that are currently specified via the SPC can be extended to cover non-marketed diagnostic testing by commercial laboratories. At present, the EMEA is not qualified to intervene in such situations.

The EMEA considers that tensions emerging because diagnostics are approved at national level and drugs at EU level have dissolved because experts from national agencies responsible for approving diagnostic tests are invited to attend EMEA briefing meetings. But care was taken to distinguish this process of integration from harmonisation, with "integration" viewed as a process of "becoming one instead of two in certain aspects, in certain tasks". As the EMEA spokesperson put it:

"So I think when you put people around the table, and you start sharing consideration, this [leads] to sharing of procedures. [and] when the time is mature, maybe [the] sharing of a framework."

Overall, the expectation is that in future the EMEA will contribute to assessment of the diagnostic component of a "PGx product" in terms of clinical relevance and utility of the test to integrate the specifications and information on both drug and diagnostic, and that this will be done in collaboration with national authorities.

4.2.4.6 EMEA and emerging therapies and technologies

The EMEA recently established a dedicated forum for dissemination of information related to efforts to encourage "emerging technologies", which include tissue engineering and gene and cell therapies as well as pharmacogenetics. According to the Agency, following "consultation with the European Commission, scientific input of experts from all EU Member States and international cooperation, the EMEA actively supports scientifically sound development of emerging therapies so that they might be made available for the benefit of public health".[126]

125 EMEA (2004) "EPAR Erbitux Abstract", available online at: http://www.emea.eu.int/humandocs/Humans/EPAR/erbitux/erbitux.htm. (Accessed on 16.5.2005). EMEA (2004) "EPAR, Erbitux, Annex 1 – Summary of Product Characteristics", available online at: http://www.emea.eu.int/humandocs/Humans/EPAR/erbitux/erbitux.htm (Accessed on 26.5.2005).

126 http://www.emea.eu.int/htms/human/itf/itfintro.htm, accessed on 16.5.2005.

To this end, the EMEA recently established a number of scientific committees, working parties and expert groups to contribute to providing scientific information in these areas. One of these – the EMEA Innovation Task Force (ITF) – was set up recently to ensure EMEA-wide coordination of scientific and regulatory expertise and to provide a forum for early dialogue with applicants. As indicated elsewhere, this development parallels the establishment in the USA of the FDA's Interdisciplinary Pharmacogenomics Review Group (IPRG) and the Voluntary Genomic Data Submission (VGDS) scheme, although it not possible to judge how similar these initiatives are without greater access to both agencies.

In addition, a number of procedures are available at the EMEA to support applicants in the development of new therapeutic approaches. These include procedures for the designation of orphan medicinal products and for the provision of EU-wide CHMP scientific advice on tests and trials to be conducted during development.

The EMEA also offers to arrange briefing meetings with applicants, to provide advice on the classification of medicinal products (regulatory classification) prior to their submission for scientific advice, orphan medicinal product designation or marketing authorisation procedures. These are somewhat similar to the FDA's voluntary data submission scheme (VGDS),[127] although it is unclear at this stage whether the EMEA intends to examine submitted data to the degree envisaged by the FDA.

4.2.5 Challenges raised by PGx from the EU perspective

The EMEA has taken a series of measures to prepare for PGx, including increasing the scientific capacity available to the Agency and introducing knowledge management activities.

According to the EMEA, no specific challenges are posed by PGx products and PGx testing in the European context. PGx technology will present similar challenges to other emerging new medical technologies, such as treatments based on cell and gene therapy and tissue engineering (EMEA respondent).

Some observers claimed that differences in EU legislative frameworks for drug and diagnostics approval could potentially pose problems in terms of PGx development and clinical introduction in the European context. Such claims were dismissed by the EMEA as the IVD Directive is committed to resolving any potential difficulties concerning the separation of responsibilities for drugs and diagnostics between the European and Member State levels.

With regard to the drug development process, as noted in Chapter 2, potential scientific and regulatory challenges associated with the co-development of a drug and a diagnostic have been highlighted by the FDA, with a call for "careful coordination" of parallel development of a drug and a diagnostic.[128] How such development will be coordinated in the context of the EMEA and the European regulatory model, with its different legislative frameworks, is not yet clear.

4.2.6 Regulatory frameworks for PGx in Member States

4.2.6.1 Approval of PGx products

As discussed, PGx applications consist of a pharmaceutical/diagnostic test combination. One prerequisite for granting safe applications in this new field is an effective approval process. So far, no specific process for approval of pharmacogenetics applications has been designed in any of the countries analysed. In, Europe the national agencies in Ireland, the Netherlands, the UK and Germany have received little direct demand from

127 FDA (2004) Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products, US DHHS, Food and Drug Administration (March); FDA News (2004) FDA Approves Erbitux for Colorectal Cancer, press release. Available online at http://www.fda.gov/bbs/topics/NEWS/2004/NEW01024.html. Accessed on 16.5.2005.

128 FDA (2005) "Drug-Diagnostic Co-development Concept Paper – Preliminary Draft", DHHS, FDA, April, available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf. Accessed on 25.4.2005.

sponsors in relation to PGx. Indeed, it appears to be more by accident than by design that the PGx products emerging at present correspond to those therapeutic areas where submission to the European centralised licensing procedure is already mandatory.

The first country to introduce HER2 testing in Europe was Switzerland in 1999. In 2000 Herceptin (trastuzumab) was introduced onto the European market. As a monoclonal antibody, it was approved by the centralised European procedure. Germany (Paul Ehrlich Institute) and Denmark (rapporteur) served as the reference countries and were therefore the first countries in the European Union to apply Herceptin in clinical settings in 2000.

GERMANY

In Germany, different authorities are involved in PGx. The Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Federal Institute for Medicinal Products and Medical Devices) is responsible for the approval of pharmaceuticals. The Paul Ehrlich Institute (PEI) is responsible for in-vitro diagnostics. Since 7 December 2003 validation of in vitro medical devices has to be conducted in accordance with the European IVDD Directive (98/79/EC). To comply with these standards, the PEI has established a testing laboratory, called PEI-IVD. Since 2000 this reference laboratory has been accredited in line with the DIN EN 17025 standard and Directive 98/79/EC to guarantee high-quality testing of medical devices. Both authorities can be concerned with PGx applications.

Herceptin is still the only application coupled with a compulsory diagnostic test. Therefore, the PEI has already been confronted with the topic. According to statements by members of the Institute, the current procedure is to examine the pharmaceutical for quality, efficacy and harmlessness, as dictated by the standard procedure. If it emerges from clinical studies, or is even known beforehand, that only a subgroup of the whole population benefits from the medication or that the dosage has to be adjusted to the individual genotype, one basic pre-requisite is the existence of an appropriate validated method that allows identification of the relevant subpopulation. An "academic assessment" within the general assessment of efficacy of the pharmaceutical evaluates data from clinical trials on the sensitivity and specificity of the test in question, i.e. a reliable method has to exist on the market that can be applied in the clinic.

One criticism levelled at the current regulation is that authorities may not, according to existing law, impose the use of a specific test on the physicians. Apart from assessing whether an, in principle, appropriate test exists, the authority's "hands are tied". This leads to the problem of remarkable differences in the quality of the tests conducted. This is a big disadvantage compared to the US regulation, where both drug and diagnostic test are approved by the same authority. This seems to be an EU-wide problem (see section 4.2.5).

Moreover, the list of devices in Annex II to the IVD Directive is not all-embracing. Specifically, methods applied for current pharmacogenetic purposes are not included and therefore need not be validated according to this Directive. This should be adjusted, according to the expert interviewed.

In the case of the BfArM, the procedure seemed to be fairly similar. The authority stated that two completely different issues and separate procedures are concerned. Standard procedure was to approve the pharmaceutical and to refer to an existing validated test. It was emphasised that the relevant test needs to be validated beforehand. In unclear cases, feedback with the validation authority formerly responsible was considered.

As an example, the person interviewed referred to other cases of products/test-kits where the authority responsible for validation of the test was recontacted to clarify the case, such as in the case of one asthma pharmaceutical and affiliated spacer, referring to the regulations in MEDDEV 2.1/3 rev 2 of July 2001, section C. For combination

products (medical devices that contain an active ingredient), a special obligatory procedure exists for consultation between the approval authority and the validating authority. However, no similar procedure for PGx products is envisaged.

Companies that have experience with the German approval procedure described the situation as good and consistent. Roche said that everything went smoothly during the approval process for Herceptin®. As there was already a certified HER2 test on the market (DAKO HercepTest) that was also applied within the clinical trials and has proven to be effective, no further problems arose within the approval procedure. Companies do not believe that any hurdles will block the way to new marketable products. The work of the relevant authorities in Germany was consistently generally approved by industry.

As we are talking about "mere probabilities" according to one respondent, companies tend to hesitate to deny access to a specific subgroup and prefer to reduce the average dosage recommendation to a middle-of-the-road compromise as long as possible. This procedure is open to criticism on two counts. First, this might be contrary to the declared aim that pharmaceuticals have to be applied economically and, second, it has to be ensured that physicians consider possible severe outcomes.

IRELAND

The Irish Medicines Board (IMB) is responsible for ensuring the quality, safety and efficacy of medicines and medical devices available in Ireland and participates in systems designed to do that throughout the European Union. The IMB recently appointed a member of its staff as the person responsible for pharmacogenomics. However, as yet no request has been made by any applicant company for assistance in this area. The IMB is not aware of any immediate product approval request that could require consideration as a pharmacogenetic product. The IMB plans to participate fully in EMEA policy discussions and other activities on this issue.

The use of medicines for clinical research purposes also falls within the IMB's remit. Clinical trials are governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 (Statutory Instrument No 190 of 2004).[129] These Regulations transposed into Irish law Council Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The NSAI was also designated by the IMB as a notified body for in-vitro diagnostic medical devices (98/79/EC). This includes Annex II List A virology products, Annex II List B products and self-test devices.

As in the IMB, no request has been made to the NSAI for assistance and no initiatives have been started by NSAI in this area. It will be watching developments, but as yet sees no demand for changes in its services or activities as a result of PGx.

NETHERLANDS

Market access for new pharmaceutical products in the Netherlands is mainly covered by European regulations that are implemented in the Dutch Medicines Act. The Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen – CBG) is the Dutch authority responsible for evaluating and issuing market authorisations for pharmaceutical products, including diagnostics, in the Netherlands. Its tasks are set out in the Dutch Act on the Provision of Pharmaceuticals. CBG also determines

129 http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040878.pdf?direct=1

whether pharmaceuticals will be registered and whether or not they should be made available on prescription.

Pharmaceutical products are evaluated on the basis of criteria defined in the Medicines Act; the criteria mainly address efficacy, safety and quality. The CBG carries out the evaluation on the basis of extensive dossiers submitted by the pharmaceutical companies, containing the required information from research studies. Medicines can enter the Dutch market after the Medicines Evaluation Board has registered them and formulated the text for the label containing product information and instructions.

Market access of diagnostics tests became regulated in the Netherlands with the implementation of the European Directive 98/79/EC on In Vitro Diagnostic Medical Devices by means of a "General Rule of Management" (Algemene Regel van Bestuur). The Decision on In-vitro Diagnostics (Besluit In vitro-Diagnostiek) was published in 2001. Diagnostic kits, such as the HercepTest™ by DakoCytomation, fall under this Decision. The fact that the HER2 test can be used in relation to prescription of a specific drug did not give it any special status in this procedure.

Unlike in the USA, market approval of DakoCytomation's HercepTest™ and of Roche's Herceptin was not combined in the Netherlands. The CBG spokesperson said that this had been discussed during the approval procedure for Herceptin, but because other HER2 tests were also in use, it did not want to exclude them (CBG 1). On the label of Herceptin reference was made to use of an HER2 test, but no specific test was mentioned. The CBG therefore focused on the required level of protein expression above which Herceptin had to be used and not on the specific test for measuring these levels.

In 1999 DakoCytomation became the first company to place an HER2 test on the Dutch market. Later it was followed by Ventana Medical Systems. The Netherlands Cancer Institute (NKI) was already using a "home brew" HER2 test on an experimental basis in 1997.

UK

Regulation of medicines in the UK is the responsibility of the Medicines and Healthcare products Regulatory Agency (MHRA).[130] The primary UK legislation is the Medicines Act 1968, but membership of the EU means that most significant regulatory legislation and procedures emanate from Europe. As in other Member States, UK medicines regulation or the impact of regulatory activity on PGx developments cannot be reviewed outside the context of EU regulation.

Like several other regulatory agencies, the MHRA relies on user fee income and is responsible for its own budget. Also, since April 2003, the MHRA has been responsible for both medicinal products and medical devices – a phenomenon seen in other Member States in recent years.[131]

MHRA decisions are based upon scientific advice provided by an expert advisory committee, the Committee on Safety of Medicines (CSM) aided by several specialist sub-committees. Measures to abolish the CSM along with the Medicines Commission and replace them with a new Commission for Human Medicines were introduced in April 2005. The changes will remove industry's representatives from the MC and set up several more expert working groups. Because of the growing complexity of drug development, the UK government also intends to introduce a greater degree of expertise at an earlier stage in the development process and greater transparency.

130 The MHRA was formerly the Medicines Control Agency (MCA). Following integration of responsibility for drugs and devices, the Agency became the MHRA in 2003.

131 In the USA, the FDA has been responsible for drugs and devices for many years.

4.2.6.2 Regulation of clinical testing services - Quality issues

There are no common statutory regulations specifically for pharmacogenetics in the four EU countries studied. However, the general accreditation procedure also applies to PGx-related activities.

The IVD Directive makes it compulsory for companies to certify their products before introducing them on the market to safeguard patients, as well as users and third parties (Article 1). This ensures a minimum standard in devices used in laboratories all across the EU. Any company introducing a non-validated test would incur a penalty.

However, regulation of the service offered by laboratories varies greatly between Member States, with different requirements for laboratory accreditation, licensing and external quality assessment schemes in place.

With the wider dispersion of the tests, quality aspects gain in importance and will result in a more complex interaction between the attending oncologist and a third party, either the clinical pharmacology or an external lab. The resultant time lag often mentioned can be ignored, according to one expert, given the fact that this is not emergency medication and that a lead-time to evaluate the alternative treatments in such severe diseases as leukaemia is always calculated.

One much-debated theme and source of quality deficiency is the current lack of communication between the laboratory physician and the attending physician. Due to the multiple relations that exist both between gene mutations and exogenous factors or between endogenous factors, it is often the laboratory physicians who are better educated and who possess the latest knowledge. They should be part of the decision-making process on which tests to conduct and to choose between all possibilities concerning the right alleles to examine. A wide range of TPMT mutations are known, but only three are usually tested. Officially approved test kits are not binding for any test. As the commercial test kits are purportedly very expensive, laboratories try to avoid using them. In the case of HER2, one laboratory reported that only HER2 antibodies are purchased from official certified producers, whereas the rest, namely the colouring antibodies, are "home brew". According to in-house estimates by DakoCytomation, the market share of procured complete test kits is only around 20 to 25%. In the case of home brews, unified certification standards would be necessary.

HercepTest™ on the Dutch market has become an issue for the Dutch regulators. The Dutch case study reports on HER2 testing mentioned complaints by DakoCytomation about having to label products that fall under the abovementioned Decision (Article 2) while "home brew" HER2 tests have no such obligation. The quality of such "home brew" tests is being questioned by DakoCytomation. This is, of course, also an issue for industry, as almost 50% of all diagnostic tests used in the Netherlands are home brew tests (C 1, C 2). In the case of HER2 tests, it was mentioned that – due to the high price of the HercepTest™ and the Vysis FISH tests – roughly 40% of the laboratories in the Netherlands that perform the IHC test use the HercepTest™, while another 10% use the Ventana test; the remaining 50% of HER2 testing is home brewed.

Quality is the weapon which DakoCytomation is using in its battle against laboratories that use the "home brew" tests. Because its test is FDA-approved and IVD-labelled[132] (under Directive 98/79/EC on In Vitro Diagnostic Medical Devices) it is in a strong position. DakoCytomation argues that an FDA-like organisation is missing in the Netherlands and pathology laboratories are not even under any obligation to keep to GLP (Good Laboratory Practice) guidelines.

132 According to the Directive, IVD manufacturers are under an obligation systematically to review the experience gained from the IVDs they have placed on the market; to implement corrective action if necessary; and to report incidents, near-incidents, and recalls to the competent authority (http://www.devicelink.com/ivdt/archive/03/09/001.html).

In the UK the CE mark is administered by the MHRA. Clinical laboratories wishing to apply for a CE mark for their assays and the services they are used to support must provide the following evidence in a technical file (equivalent to about four large A4 ring binders) which is reviewed by the MHRA:

Essential requirements checklist:

- Data section – describing methods used, and standard operating procedures;
- Risk analysis exercise – ensuring steps have been implemented to minimise failures;
- Reagent manufacture controls – best before dates and audit trail;
- Vigilance system – processes to ensure errors are detected;
- CE declaration of conformity.

One laboratory which had been through this process reported that it was time-consuming, but that the experience would not put it off applying for further CE marks on its other assays. It suggested that previous concerns of laboratories that the IVD Directive would restrict their ability to operate in the future may have been unfounded. Although the CE mark was not intended to be applied to NHS laboratories, it could have an impact on the robustness, both in terms of quality and delivery, of such services there.

In the UK, despite the exemption provided to clinical laboratories by the MHRA's interpretation of the IVD Directive (see section 8.3), clinical labs may consider participating in the CE review process to obtain approval for assays produced in-house. In particular, NHS laboratories are increasingly behaving like commercial entities and expect the CE mark to provide added value to their services.[133] A CE mark puts these laboratories on a level playing field with industry kit producers in terms of the regulatory burden on product quality and could open up opportunities for them to provide services to industrial partners.

Some respondents noted that there appears to be a regulatory gap in the provision of diagnostic testing services in hospital laboratories because although kit manufactures must abide by the IVD Directive, there is nothing to stop hospitals from buying kits or reagents that are not intended for medical use (lab 6). For example, in the field of genetic testing services for conditions such as cystic fibrosis, the Applied Biosystems Inc. oligonucleuotide ligation assay kit marked for "research use only" is routinely used by laboratories (lab 4). Even when CE marked kits are used by laboratories, there is nothing to prevent the laboratories from deviating from the protocol. For example, in HER2 testing there are still local sources of variation. Laboratory staff in different centres use different preparation methods because they are not used to methods suggested in the kit instructions. Sample retrieval methods used by clinical staff prior to the samples arriving at the laboratory also vary (lab 5). Furthermore, the cost of kits is an added incentive for staff to attempt to adjust protocols or find alternatives to commercial kits although unfortunately these practices often result in those labs performing less ably according to QA results (lab 5).

Guidelines recently introduced in the UK require that HER2 testing should be conducted only in laboratories that have an annual caseload of at least 250 cases. Given that the FISH test is applied only in cases where HercepTest results are equivocal, if a laboratory with a low caseload produces a higher number of equivocal HercepTest results, expensive FISH tests are presumably applied more frequently than would be necessary in the case of a larger regional laboratory with a higher caseload.

A variety of about 30 different commercially available antibodies can be used for IHC testing for HER2 overexpression, although in reality, even in "home brew" tests, only two or three antibodies are in common use. Unlike the USA, where the FDA has some control over "home brew" testing,

133 Berg, J. (2004) "MHRA climbdown on in-house assays", ACB News, August, pp. 4-5.

in the UK regulations are lax, with the result that it is the QA scheme which effectively "regulates" the use of different antibodies in testing. Data from the QA scheme suggest that the DAKO testing kit (used according to instructions) performs better than alternatives, and if a laboratory fails this assessment it is at risk of losing its accreditation. One of the main points stressed by the QA scheme assessors is the accuracy of the ready-bought kits.

4.2.6.3 Staff training

During the interviews it was realised that - where the theme was common at all - it was the laboratory physicians who had the latest knowledge in this field. The attending physician often did not know these correlations. Still, the physician is at the front-line and has to commission the test in question. This gap is hard to bridge.

To encourage appropriate use of PGx testing when applicable, there is a need to educate the relevant medical staff. This extends beyond experienced doctors and must include pharmacists, nurses and junior doctors wherever they prescribe drugs linked to PGx tests. Such efforts should include mechanisms to encourage the transdisciplinary spread of prescribing guidance so that the different specialities do not have to "re-invent the wheel". In similar vein, practitioners of PGx testing services based in different disciplines, such as molecular genetics and biochemical genetics and immunohistochemistry, could benefit from greater interaction to improve best practice and prevent fragmentation of this emerging field.

4.3 Industry's view on regulatory issues associated with PGx

4.3.1 Regulatory compliance as a driver for adoption of PGx

Regulatory compliance is not a major driver of PGx usage within the pharma companies surveyed. While they are undoubtedly among the drivers, no company mentioned safety or regulatory compliance as the major reason for their use of PGx. One company pointed out that one factor behind its entry into PGx was the realisation that sooner or later regulatory authorities would start looking for pharmacogenetic data. However, even in this case, this was one driver, but not the only one.

The primary industrial users of regulation of PGx-related products are large pharmaceutical companies, bio-pharma companies (biotechnology companies with a drug pipeline), diagnostic companies and service companies. Some companies produce diagnostics and drugs.

If regulatory compliance was a key driver, PGx expertise could be expected to be located within the clinical development section of companies. This is not the case in the majority of pharma companies surveyed. In most of them, PGx is established as a service unit within R&D (sometimes several service units in different R&D groups) and the skills are available to all the different R&D or clinical development teams within the company. The major users of this expertise would appear to be the discovery teams. In most companies, the clinical development staff also used the PGx team. At the basic level, this might simply consist of compiling genetic data on tissue samples so that retrospective genetic screening could be conducted if any differentiation of effect between patients is found in the trial process. In other companies, the PGx team was available to "rescue" clinical trials. The PGx unit is controlled by the clinical development team in only a small minority of the companies surveyed.

In addition to pharma and diagnostic companies, service companies were also surveyed (see Table 1.1). Once again, none of these companies mentioned regulatory issues as a major reason behind client demand for their services.

4.3.2 Social/ethical barriers to use of PGx

No company had experienced any patient resistance to PGx products in trials. Instead, several companies noted the disconnection between the perceived view of ethical groups regarding DNA testing safeguards, and the practical experience of seeking patients' agreement.

Several companies noted, however, that the consequences of perceived ethical issues with genetic materials were the introduction of legislation and rules at all levels. This has resulted in practical and administrative difficulties for the PGx discovery and development process. This is particularly so in the EU, where the variation in legal requirements between Member States forces companies to comply with a wide range of legislation. In practice, this may mean that batches of samples from different EU countries must be treated differently in terms of the sample collection and consent process, the data that may be collected, and the way in which both data and samples are stored. This adds a great deal of complexity to an already highly complex data-handling process and can be regarded as an additional impediment to implementation of PGx in the EU, as compared with the USA and Japan. It might, for instance, be necessary to develop different array systems for samples from different countries because of variations in the data which it is permissible to collect from specific samples.

The "constant discussion" on the need for further legislation also creates uncertainty about future data handling needs. Although companies insisted that they would fully comply with all legislation, the diversity of EU requirements clearly creates difficulties that are not present in the USA.

4.3.3 Regulatory differences between the EU, the USA and Japan

Few respondents had experience of Japan, although one company noted that Japan has no problem with the concept of genetic testing.

There was a clear view that the EU was a far more difficult place to work than the USA. In the words of one respondent, the EU is a "logistical challenge" for pharma companies. The differences affected several aspects of company operations:

Samples and testing: The EU was almost unanimously regarded as a difficult place to conduct clinical research, and certain countries (e.g. Sweden and France) were cited as examples on several occasions. The major concern was not that provisions were in place to safeguard patient rights, or to define protocols for sampling or for collection, retention or use of samples. All companies stated that they were very willing to comply with local legislation. The concern centred on the big differences in the detail of these provisions between countries, and the fact that they were continually changing. One company noted that new rules continually seem to "pop up" and that constantly trying to comply with the resulting procedural changes was a "pain in the neck".

EMEA and FDA: The majority view was that the FDA had "got its act together" on PGx drug regulation and was pro-actively engaging with industry and others in defining a regime for approval of PGx drugs. The FDA was seen as having actively organised meetings with relevant parties, including industry, to brief itself on the issues. It had then set about defining guidelines for submission of data, again with extensive inputs from industry. These guidelines have now been launched. The EMEA, on the other hand, was seen as lagging behind in this process and not being as aware of the issues as the FDA.

Some companies felt that the EMEA's apparent position of waiting and watching might have some advantages as it could learn from the FDA's experience. This was seen as allowing EMEA some flexibility in defining PGx regulations. However, it was difficult to see how it could put the EU in a position to review PGx drugs as early as the FDA might.

Comparative views of the two agencies included:

"The FDA is more interested [than the EMEA] in the science."

The EMEA is "slower and more conservative than the FDA."

The FDA is proactive and engaged with clinicians and industry. This was not felt to have occurred in the EMEA as yet.

The FDA has been "moderately enthusiastic" about PGx and has provided mechanisms to support data submission. (Respondent did not see the same attitude from the EMEA).

"The FDA is actively looking at the issues and staying abreast, whereas the EMEA is only watching".

One company noted the possibility of a major PGx skills shortage occurring in EU regulatory agencies as a result of the lack of appreciation of the different regulatory approach required.

"Most of the discussion with the EMEA was about ethical issues rather than regulatory issues" whereas the FDA position on ethical issues was clear.

Sources of PGx expertise: Two pharma companies noted, in different contexts, that the major source of activity and expertise in PGx is in industry. This suggests that regulatory authorities must engage with industry to understand current developments in the field. While the FDA has done so, the EMEA is reportedly less engaged with industry in PGx. In addition, respondents realise that the EMEA intends to source a significant proportion of its advisory input from academia. While academic institutions are very involved in research on disease genetics, they are not generally engaged in research on drug response genetics. They "know the science" but may not have a good feel for the practical issues surrounding drug development and approval.

Diagnostics: Two diagnostic companies noted that the regulatory approach to their products was often very different between the EU, the USA and Japan. A product that is regarded as a simple device in one country may be regulated at a higher level in another. This, however, is not specific to PGx and can occur in any Dx product.

Patents: One company noted that there was greater clarity in the USA on use of patented genes in clinical trial data submitted for regulatory approval. Interpretation of patent law in this specific area is less clear in the EU.

4.3.4 Harmonisation of regulation

The issue of global harmonisation evoked a wide range of opinion, which is surprising considering the relative consensus on the above issues. There were effectively three "camps" in this discussion:

- those who felt that the FDA and EMEA must engage to harmonise regulatory provisions and were disappointed with the different rates of progress of the two agencies;
- those who, while welcoming harmonisation, felt that tended to make the regulations less amenable to change. This group felt that it might not be useful to seek harmonisation too early in the process of development of a regulatory framework;
- those who did not believe that harmony would ever be achieved. "It would be nice, but it will never happen."

4.3.5 Regulattory needs expressed by industry

There was a general consensus from the companies that the main need was for clarity in the legislation, i.e. that firms have a clear basis on which they can plan their regulatory approach in the PGx area. The same general principle applied to their needs for regulations on sampling and biobanks. Several companies said that final planning on their regulatory approach was on hold until they had reviewed the regulatory guidelines which emerge.

Comments on this issue include:

"We need to know what to comply with."

"It is important to have an agreement on basic principles, such as sample and data management and informed consent procedures. For example, there needs to be an appreciation of and consensus on: the terminology used for coding samples and data for confidentiality purposes; where, and for how long, samples and data are stored; the scope of research required for key exploratory work."

"Trial needs (between countries) may vary which is very frustrating as [trials] could be planned from the start if regulations were clear."

"The major challenge [facing industry with regard to regulatory approval for pharmacogenetics-based drugs] is clarity of regulatory approach."

Table 4-1: Selected regulatory factors that may influence successful diffusion of PGx technolog

Topics	USA	UK	Netherlands	Germany	Ireland
Regulatory framework for PGx drug development	New internal structures created by FDA to support PGx development. New guidance on regulatory submissions developed with industry. Voluntary submissions system for exploratory data. No plans for compulsory submission of PGx data	**EU-LEVEL** - The EMEA (the European regulatory authority for medicines) has created new internal structures to support PGx development. Guidance provided to sponsors through briefing meetings. No plans for compulsory submission of PGx data.			
		No special actions taken in relation to PGx beyond staff appointments. Issues such as sample storage and data storage in relation to genetic data and Informed consent are under consideration. No immediate likelihood of requiring genetic data for all new drug MAAs. Cautious of creating 'orphan' patient subsets.	No special actions, beyond establishment of working group. No relevant drugs are being developed in Netherlands at present.	No special actions taken in relation to PGx as existing frameworks seen as sufficient. No immediate likelihood of requiring genetic data for new drugs.	Other than appointing a staff member to follow PGx, no special PGx measures have been established for drugs/ devices. No notifications by drugs or device firms made in Ireland regarding PGx.
PGx data and drug labelling	Incorporation of PGx data in drug labels underway.	**EU-LEVEL** - EMEA incorporates PGx data in drug labels (e.g. Herceptin, Erbitux) and has power to revisit old drugs to re-label. .			
		No current plans to re-examine previously licensed drugs– more likely to be undertaken at EU level.	Regulators are keen to reappraise previously licensed drugs where PGx data emerges.	No current plans to re-examine previously licensed drugs.	**No action at present**
Commercial incentive to create drugs for sub-populations?	Orphan drug legislation in force.	Orphan drug status available via EU legislation	Orphan drug status available via EU legislation	Orphan drug status available via EU legislation	Orphan drug status available via EU legislation
Regulation of PGx diagnostics	No special conditions for PGx tests. FDA reviews marketed tests, but not analyte specific reagents. Manufacturers of marketed tests claim playing field is not level as 'homebrews'* are not required to submit to FDA. Use of FDA approved tests is not mandatory for hospitals.	**EU-LEVEL** - EMEA has no legal jurisdiction over In Vitro Diagnostics (IVDs) – approval resides with member states. However, assessment of PGx drug-test package would be undertaken by EMEA when submitted together for approval via centralised procedure. The EU IVD directive aims to harmonise framework for approval of diagnostics, including PGx tests. Tests that conform to standards are awarded the CE mark. Manufacturers are required to show analytical validity but not clinical validity to gain CE mark.			
		No special conditions for PGx tests. CE Mark required for marketed tests but not for home brews (hospital labs are exempt). There is some industry concern over the lack of a 'level playing' field, due to different regulatory treatment of 'homebrews'. Use of CE marked tests is not mandatory in hospitals. Reagents and equipment for 'Research use only' viewed as important tools for clinical testing by users.	No special conditions for PGx tests. CE Mark needed for marketed tests but not for home brews. Industry claim playing field is not level in diagnostics Use of certified tests not mandatory in hospitals.	No special conditions for PGx tests. CE Mark needed for marketed tests but not for home brews. Use of certified tests not mandatory in hospitals.	No special conditions for PGx tests. CE Mark needed for marketed tests but not for home brews. Use of certified tests not mandatory in hospitals.
Framework for regulation of drug-test combinations	The FDA undertakes both diagnostics and drug approvals and encourages co-development of PGx drug and test when appropriate.	**EU-LEVEL** - EMEA has no legal jurisdiction over In Vitro Diagnostics (IVDs) – approval resides with member states. However, in practice drug-test combinations would be assessed as a package by EMEA to enable drugs to be approved with appropriate labelling.			
		One joint authority (MHRA) regulates devices and drugs but distinct groups handle each. The national diagnostic approval contrasts with centralised EU drug approval for many innovative medicines. This has not been problematic to date (e.g. with Her-2 and Herceptin).	One national regulator (CBG) undertakes devices and drug registration. Separate applications for PGx diagnostics is encouraged to allow multiple tests to be marketed.	Drugs and devices still overseen in distinct regulatory bodies (e.g. Her-2 test and Herceptin not considered together). PGx seen as a challenge, but handled satisfactorily to date.	Although drugs and devices regulation in one organisation, distinct regulatory groups remain and approvals are not linked. No requests have been made in Ireland for drug-test combinations to be jointly approved.

Table 4-1: Selected regulatory factors that may influence successful diffusion of PGx technolog (cont.)

Topics	USA	UK	Netherlands	Germany	Ireland
Accreditation laboratories offering testing services	Certification of laboratories (awarded after site inspections) is a legal requirement for service laboratories under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) - as well as specific laws in some states. Federal CLIA certification is legally enforcement with fines and closures. CLIA is administered through the Centers for Medicare & Medicaid Services College of American Pathologists (CAP) also offers a more stringent inspection and accreditation scheme.	Accreditation (awarded after site inspections) is increasingly required in the National Health Service – but passing inspections is not expected to be mandatory for some time.	Accreditation schemes are long established but still not mandatory and there are no financial consequences for laboratories that are not approved.	Accreditation is being established but not fully implemented at present. Currently no consequences for non-approved laboratories.	Accreditation is not universal in Irish labs at present, but many have CPA approval and are subject to qualifications standards for staff.
Proficiency testing (Quality Assurance)	Proficiency schemes run by CAP can be for educational purposes or 'graded'. Failure of a 'graded' scheme leads to withdrawal of CLIA certification for a given testing service.	Well-established QA schemes with high participation in many diagnostic fields. QA failure can lead to withdrawal of CPA accreditation for all laboratory activities. However in practice, QA schemes exert weak regulatory pressure, but do boost learning and performance.	Well-established QA schemes exist, but participation is not mandatory.	Some schemes exist but participation is not mandatory.	PGx is not seen as a separate area of professional practice. Proficiency testing exists in most of the analytical and clinical fields of relevance to PGx. Many labs are also affiliated to UK schemes due to small local scale.
Proficiency testing (QA) schemes for PGx	No graded proficiency testing schemes for PGx, although Her-2 proficiency testing is well established.	UK is a base for several international QA schemes, including PGx schemes for TPMT testing and Her-2 testing.	PGx is not seen as a separate area of professional practice by laboratories. There are no Dutch PGx QA schemes	PGx is not seen as a separate area of professional practice. There are no annual schemes for PGx tests at present. If a laboratory is accredited there is the obligation to participate regularly to inter-laboratory schemes.	There is no Irish QA scheme specific to PGx – but laboratories join UK schemes/ European schemes.
Reimbursement of testing services	For federal monies, only pay CLIA certified labs. However some non-CLIA research labs offer services (and may be asked to desist from doing so) warned. Laboratories have to seek reimbursement for specific tests from individual insurers, and often reimbursement is not sufficient.	Local decisions made by hospitals, although high profile cases reviewed by National Inst. of clinical Excellence to ensure less inequity. Some national concern that limited reimbursement of HER-2 testing may be effectively rationing Herceptin.	Case-by-case decision made by individual hospitals regarding reimbursement for drugs (depending on budget available). Tests are reimbursed by hospital user.	Joint federal committee of the health ministry judge what is reimbursable by health insurers. Genetic tests have had difficulties in gaining reimbursement in recent years. As a result Roche reimburses FISH testing costs for HER-2 testing. Immunoassays are reimbursed more commonly.	Most tests are reimbursed without formal process, by private or public insurance as numbers of requests are small.

Table 4-1: Selected regulatory factors that may influence successful diffusion of PGx technolog (cont.)

Topics	USA	UK	Netherlands	Germany	Ireland
Clinicians awareness of PGx and education levels	Little usage of PGx outside oncology. Poor educational base. Several professional-led initiatives to improve situation but limited to some centres of excellence.	Significant variation in PGx use across medical disciplines using TPMT testing. Professional bodies seen as having a key role in addressing this problem. Little interest in PGx overall amongst physicians.	Variation in PGx use across medical disciplines – mainly due to cost of drugs such as Herceptin.	Patchy but growing awareness of PGx. Poor educational base at present results in difficulties in communication between lab and doctor. Medical schools now include limited PGx training for all new doctors. Usage mainly in oncology and CYP450 metabolism.	Level of awareness of PGx varies between hospitals. New clinical appointees (due to expansion & redesign of health system) have increased awareness of PGx.
Special genetic legislation	Anti-genetic discrimination law has been in preparation for some years but yet to be made law. Need for genetic testing guidelines to support CLIA – these are in development at present.	Moratorium on use of genetic information in insurance in effect. Human Genetics Commission proposed a law preventing genetic testing without permission, no government response to date.	Legal protection of patient freedom of choice and privacy exists but no special legislation proposed to cover genetic testing.	No specific regulations or law, other than against misuse of genetic tests. A draft law is in preparation on genetic diagnostics.	No specific legislation has been initiated. An insurers' code of practice regarding use of genetic information is in place.
Ethical and social concerns (illustrative – and not necessarily comprehensive or exclusive to particular countries)	PGx seen as low threat, compared to issues raised by other genetic tests.	PGx seen as ethically unexceptional – although informed consent is reportedly often neglected prior to TPMT testing and HER2 testing, due to time pressures or the perception by doctors that patients are more concerned with the seriousness of their condition than the implications of diagnostic tests.	PGx is positively assessed by patient organisations. Informed consent in case of genetic testing was a concern raised by them also. There is wider concern about impact of genetic tests when sold directly to consumers.	In general PGx testing met approval, and PGx info often seen as comparable to other diagnostic information and as not as problematic as other genetic data. Yet concerns raised by patient groups and clinicians included: Informed consent, protection from discrimination, right not to know, Concerns about supplementary information on disease predisposition.	No major concerns other than doctor liability if adverse drug reaction occurs (due to litigious environment).

Source: National case studies based on review of policy literature and interviews with a range of stakeholders.
**A 'homebrew' is a non-marketed test used within the laboratory/ institution of origin.*

5. Conclusions

In order to gain a comprehensive picture of the field of PGx in Europe, without ignoring the situation in the USA and Japan, a thorough search was conducted that included several search engines, press reviews, publication databases, university listings, analysis of company press releases, various industry databases and patent analysis. A list of 264 public research organisations and around 300 firms working in the genomics field were identified. There are 47 core SMEs focusing specifically on PGx, 18 SMEs with a minor interest and 16 large firms. To specify the objectives of PGx research in greater detail and gain insight into the frame conditions for research, such as financing, networking and collaboration between academia and industry, the research teams identified were asked to participate in an online survey (altogether 60 answer sheets could be analysed). The information compiled from desk research and the online survey was verified and completed by questionnaire-guided telephone interviews with management staff from 15 leading companies and researchers from six of the high-ranking research organisations identified.

It is clear from the study that PGx is an important and growing field of interest in the scientific community both in Europe and in the USA. Well-known centres of excellence can be found on both sides of the Atlantic and knowledge transfer by international conferences is good. Japanese scientists are also involved in PGx research with a number of internationally known research groups. However, Japan places the emphasis on Asian ethnic groups and its research has a more national character.

The private sector was dominated by clear US industrial leadership in the small firm stakes in the early 1990s. However, a high attrition rate amongst small firms and disinvestment by many combined with increasing industrial activities in Europe since 1998 reflect the high technological uncertainty in the field. Large firms invest to varying degrees.

The EU is well-placed in PGx research, but is lagging behind in industrial activity.

Most companies see PGx as a useful tool in the drug development process and not necessarily with a PGx diagnostic test as the end-point. However, the actual utility of PGx in drug discovery remains to be seen. Only diagnostic companies (around one third of the total number of companies involved in PGx) see a pure market for PGx products. A patent analysis confirmed that very few patents are meant for direct PGx products. Moreover, only 50% of the large firms investing in PGx in Europe and the USA held any PGx-related patent which signals that, in terms of commercialisation, PGx science is still immature. As methods are expensive and not everyone agrees on the robustness of the tools as yet, great efforts remain to be made. As a result, at present a great deal of research is in progress, many genes are being examined for PGx, but few products are being applied on the market.

Public research groups are devoting equal efforts to basic and applied research, focusing on elucidation of basic mechanisms and diagnostic applications. Commercial interest in PGx is spread across the whole process of drug discovery and development, with little commercial interest in drug rescue (either safety or efficacy), market extension strategies, post-marketing surveillance or the use of efficacy data in drug marketing. Within the development process, use of PGx in clinical and pre-clinical trials, focused on both safety and efficacy, is attracting the most interest. Firms interested in development of PGx tests are almost entirely focused on diagnostic tests.

A patent analysis provided insights into upcoming products. Various cancer indications

seem to be generating the greatest activity, followed by other widespread health problems such as cardiovascular disease, obesity, diabetes and asthma. Future PGx products mentioned in the interviews were mainly oncology tests (based on tumour classification) and other diagnostic tests that are close to, or are already, being marketed. This shows an interesting trend towards an overlap between PGx and traditional genetic diagnostics and it is becoming almost impossible to draw a dividing line between them.

The analysis showed that most PGx applications will have an impact on the drug development process which will affect the pharmaceutical industry while patients will be less directly influenced by the tests. Also, in contrast to earlier predictions, PGx does not seem, for the time being, to be playing an important role in reinvestigation of drugs that have been dropped due to low safety or efficacy. This trend might change once the advantages of PGx become more obvious.

PGx science is still immature and has not yet delivered its potential. Research tends to focus more on what PGx can provide for drug development than on diagnostics for "personalised" medicine.

Interestingly, there seems to be agreement about the poor level of efficacy/safety of current drugs which gives PGx considerable scope to improve the situation. PGx is expected to lead to an overall cost reduction for health services due to fewer adverse effects. The principal medicine licensing agencies, the EMEA and FDA, have broadly positive views on the technology's prospects. The view of the EMEA expert interviewed was that over the next 20 years PGx will have a "huge impact". This will affect drug development and the strategic management of R&D pipelines, but will affect some fields of therapy more than others. This perception of uneven development appears to agree with observations made by previous commentators. The FDA highlighted the growing role of PGx in drug development, especially in sub-populations, but was more cautious about the prospects for PGx in improving pharmacovigilance given the range of causes of adverse events.

Experts from both the public and the private sectors agreed on the time-scale for PGx to make any significant impact. It has already made some impact on drug discovery and development. This will increase gradually. Most experts estimated that it would take 20 to 25 years for PGx to have a significant impact on public health. They predicted that within 3 to 5 years PGx tests could be standard practice for some indications.

Although much uncertainty remains about the impact of PGx, especially as the evidence base has yet to be developed in many areas, experts point to reduction of adverse effects as the most notable impact to be expected.

A high proportion of public research is financed by core funding from national governments. Industrial contracts and funds from foundations play a minor role and contribute only to individual projects. EU funding for PGx was used by under 10% of the research groups. Although FP6 offered the opportunity for PGx funding, researchers complained about the heavy administrative burden and unclear requirements. A strong network covering the whole area of PGx was not accepted for funding and indication-based projects were favoured according to one respondent. This appears to have discouraged many European initiatives.

Academic research in the EU could benefit from greater unification of efforts and funding of more infrastructure – ethical clearances and access to biobank collections plus systemic programme investments (PGx must be sustained over the long term as it is not going to yield results overnight).

Is EU funding being fully used? Less than 10% of the most active groups in PGx in Europe receive finance from FP6.

Most companies finance their research from their own cash flow. Some are carrying

out or have carried out publicly funded research projects (mainly in collaboration with academia). Most companies interviewed, however, stated that the administrative barriers are too high to save any money, but recognised that networking through publicly funded projects is important. Paradoxically, although none of the companies interviewed was seeking public R&D funding, almost all were very positive about their interest in becoming involved in publicly funded networks and even hire staff to monitor these activities. This could be because the funding aspect per se was not of importance to any company. Even companies which were involved in an FP activity were not aware of whether they were receiving any funding. Many companies pointed to the need to revise the public funding programmes to make it easier for companies to become involved in useful collaboration. At present programmes do not always fit their needs.

Nearly 40% of respondents in the R&D section complained about the lack of specific PGx research programmes. A shortage of human resources hinders efficient research in PGx, a criticism made by every second researcher. Finally, lack of support of the large-scale infrastructure necessary to deal with complex genomic questions is a major obstacle to efficient PGx research.

In general, the private sector values collaboration with the public sector. However, interviews with the industry showed that, for strategic and confidentiality reasons, only a small proportion of tasks can be subcontracted to the public sector. Experts from academia see the different research interests as one of the main obstacles to extension of industrial collaboration: industry appears to be mainly product-oriented following a blockbuster strategy that sees PGx merely as a tool to make drug development more efficient. There seems to be tension between the goals of researchers (understanding genetic variability) and of industry (overcoming this variability). Contrary to the opinion of the public sector, representatives of industry complain about problems with IPR matters in public-private collaboration and a lack of awareness of milestone agreements. High administrative barriers at public research organisations are also perceived as preventing industry from establishing collaboration with academia.

Another difference is the scale of research. Academic circles are only able to tackle genomic and PGx issues on a small scale, whereas industrial drug development processes require large integrated projects which can cover the genomic complexity. This explains why the private sector cooperates with the public sector on discovery projects and on the development of methods.

As a result, only one out of five European research groups collaborates with a large enterprise, mainly on a project basis. Collaboration between industry and academia might need to be better promoted by appropriate European funding programmes. At the 2004 PGx workshop a joint call was made for Commission research programmes to tackle this problem; it was agreed that it is not a matter of funding but of linking these separate sectors and increasing collaboration between them.

Academics complain about the limited access to private-sector databases. In their opinion companies' genetic sample databases would offer a huge chance for studies to link genetic markers with disease. Access to the industry's PGx trial information could stimulate research enormously.

Industry prefers to handle its own funding and finds it burdensome to obtain public incentives, establishing very few research partnerships with academia as a result. Collaboration between industry and academia might need to be better promoted by appropriate European funding programmes.

Alongside the abovementioned project-based cooperation, knowledge is transferred between the public and private sectors. In nearly 50% of all research groups researchers are also members of the advisory board of companies. Technology

transfer offices promote knowledge transfer in one third of all research groups.

In the USA and Japan the establishment of consortia forms another pillar for networking and knowledge transfer. The Japan Pharmacogenomics Consortium was established in 2003 to promote the development of infrastructure and national standardisation for conducting pharmacogenomics-related clinical trials in Japan. Through this consortium, pharmaceutical firms will be able to collaborate in solving pharmacogenomic trial issues and to develop the required know-how in synergy. In 2000 the USA initiated a major funding project in pharmacogenetics, the NIH Pharmacogenetics Research Network, to establish multi-disciplinary research groups with the purpose of developing and populating a public database. Researchers from the Pharmacogenetics Research Network are now trying to start collaboration with European institutions. One of the experts argued that this global alliance can be expected to give an additional knowledge and technology push.

As mentioned earlier, PGx is a very dynamic field. During the last five years the total budget spent on PGx activities increased in nearly 59% of all research groups answering. The average budget of the groups participating in the online survey was roughly €300 000. A comparison between research budgets in Europe and the USA revealed that US research groups have on average twice the financial resources available to European groups. Several respondents attributed this difference to the massive activities started by the NIH Pharmacogenetics Research Network. These activities were described as a means to catch up with the pioneering work carried out in Europe between 1986 and 1998 by the COST B1 programme ("European collaboration on the study of inter-individual differences in drug disposition and action"). However, in the opinion of most European researchers, the USA has achieved its goal and overtaken European research in terms of scientific output.

With regard to the core technological requirements for PGx, there was a clear consensus amongst most public research and industrial respondents that there are no major technical barriers. Problems identified include:

- Availability of samples from well-characterised patients. This is a problem in PGx research both in terms of availability of such samples and also the ethical issues surrounding the process.
- Lack of clear evidence to relate drug response to genetic status. This is the critical link and has been defined for only very few cases to date.
- In terms of access to technology, the process of identifying and negotiating rights to patents on DNA with a diverse group of owners is a major "nuisance" to some respondents.
- The high cost of PGx work, including the capital and hiring cost of setting up a PGx team, is an obstacle to PGx research. This includes the availability of well-trained human resources (e.g. in the field of bioinformatics). Small companies in particular complained about this matter as they compete with large enterprises that pay higher wages and offer "less risky" working conditions. PGx can add a high level of complexity (sampling, data management, etc.) to a clinical study which has not yet proven to be justified. The cost of genotyping can be very high and can be prohibitive.
- The bioinformatics systems were not yet adequate to cope with the huge volumes of data. Data "integration rather than interpretation" remains the challenge according to some respondents. Also, organising data collection is a problem in terms of collecting only the data approved by the ethics committee for the ongoing study, as "off-the-shelf" arrays will often collect data on other parameters. However, to devise customised arrays for every trial is too expensive.
- Some respondents stated that instrumentation and methodologies used in PGx are new and

require further development. However, this opinion was not shared by all respondents.

- The variability in the action taken by ethics committees and data protection requirements pose major barriers to PGx research, in particular when patients are recruited in several EU countries and studies have to comply with ethics requirements that differ across Member States.
- Similarly, the diversity in national practices related to data protection requirements poses an additional barrier to PGx research.

A number of factors may conspire to make academic research into PGx more difficult than commercial research. Academics wishing to undertake genetic association studies with new drugs may face reticence about collaboration on the part of industry if industry believes it could be forced to share the results of such research with regulators. Furthermore researchers report a mounting bureaucratic burden facing clinical trials undertaken in the EU, as well as increasing difficulty in meeting ethical and regulatory requirements [60]. These demands place a disproportionate burden on not-for-profit organisations with fewer resources than firms.

Access to patient populations and clinical trials of adequate size will be required to lend sufficient strength to pharmacogenetic studies. The gathering, use and storage of genetic data obtained from clinical trials raise numerous issues, such as the adequacy of protocols to ensure informed consent, patient autonomy, privacy and confidentiality. Experience from industry suggests that there is little if any patient resistance to collection of PGx data. However, it is widely acknowledged that the proliferation of protective measures and the dynamic nature of policies and guidelines at national level create challenges for firms operating in the EU. Despite their concerns about the challenge of keeping up with regulatory change, firms are keen to cooperate with best practice. Privacy and future uses of the genetic samples must be carefully balanced by clinical researchers and adequate informed consent must be guaranteed. The ethical, social and legal considerations need to keep in step with scientific progress. At present researchers tend to neglect any severe problems related to this field. However, wider use of pharmacogenetic information in the clinical setting will be possible only if the socio-economic impact is connected to scientific progress and the non-scientific issues create no barriers to actual application, thereby ensuring the availability of data on different patient populations to undertake drug efficacy and safety studies as well as harmonisation of the ethical committee standards that oversee these processes (for example, on the collection and retention of biological samples from patients in trials).

Intellectual property rights

In the USA there has been at least one case of withdrawal of a PGx test - a molecular genetic testing service for TPMT - by a hospital laboratory following enforcement of patent rights by the assignee (Prometheus Inc.). Given the extent to which public- and private-sector organisations have attempted to patent useful parts of the human genome in recent years, intellectual property rights (IPR) could become a significant barrier to provision of low-cost services by public-sector laboratories. However, this is not likely to be a uniform problem as countries such as the UK with a unified healthcare system may have significant bargaining power to obtain favourable licensing conditions. Germany has only recently recognised such patents and therefore has little experience of this phenomenon. No such concern was voiced in Ireland, and in the Netherlands the issue seems to be whether hospitals that have developed a test should themselves be focusing on patenting their research.

Potential market failure

While industry may be keen to apply PGx to support new medicines, the use of established off-patent medicines might also significantly benefit from PGx testing. In practice, the lower cost,

established profiles and familiarity of clinicians with older drugs ensure that they remain widely used long after their protection has ended. Because of their scale of use, there is evidence that they are also responsible for the vast majority of ADRs. The FDA has shown willing to revisit licences of established drugs, for example in the case of the anti-cancer agent irinotecan. The EMEA is also likely to take action wherever deemed appropriate. Where older drugs generate little revenue firms are unlikely to sponsor the regulatory process necessary to reappraise their drugs in the light of PGx data. Although the Netherlands and UK governments have funded some research on PGx and licensed medicines, it seems that at present the market for PGx tests for existing drugs needs more support to encourage research that defines groups at risk and develops drug and test combinations that make the best use of PGx in widely used off-patent medicines.

Furthermore there is a need to create incentives to make re-licensing economically feasible, although it is not clear how a single firm would benefit commercially from linking a diagnostic test to a drug if multiple generic producers were in the market place already. Creating such incentives may be the predominant means for policymakers to channel the knowledge of pharmacogenetics already gained for improving the safety and efficacy of current drugs, rather than waiting for new drugs licensed in combination with pharmacogenetics tests.

Although 50 years of public PGx research and more than a decade of strategic activities by the private sector have considerably promoted this field, PGx is still not broadly applied in the clinic. One of the reasons for this could be the technical and socio-economic barriers. In order to gain insight into the practical aspects of implementation of PGx in Europe and associated socio-economic issues, two cases where pharmacogenetic testing is already in use in clinical practice were evaluated to reveal possible economic and social issues: HER2 testing (efficacy of trastuzumab for metastatic breast cancer) and TPMT testing (safety of thiopurine drugs for acute lymphoblastic leukaemia). These two case studies provide insight into the current and past social and economic issues. Four countries were selected for these case studies: Germany, Ireland, the Netherlands and the United Kingdom. Interviews were conducted in all of them to gain a range of perspectives (including those of government health policy, a regulatory agency and a laboratory service). Several findings emerged from this review of the factors influencing clinical uptake in these two cases:

- The major role played by industry in introduction of the test was very clear in the case of HER2 testing. While in the UK and Germany industry, i.e. Roche, played a very active role in introduction of the test, in the Netherlands and Ireland other players, such as clinicians and patients, were the driving forces. To put it another way: on large markets industry actively pushes the technology, while on smaller markets this is left to the users: patients and doctors. In the UK Roche overcame the cost-driven scepticism about HER2 testing that was apparent in all four countries by funding all HER2 testing in the UK for a certain period and making Herceptin available to clinicians. In Germany Roche persuaded specific pathological laboratories to become reference centres. This made doctors familiar with the test and Herceptin. Roche also mounted a massive marketing campaign.
- In the Netherlands Roche was less active. Probably as a result, a relatively large number of "home brew" tests (developed by laboratories themselves and much cheaper) are on the market. As in the case of TPMT in the four countries analysed, dissemination of the test is not strongly promoted by a pharmaceutical company or by any other organisation, such as a patients' group. This is probably due to the small size of the market. Although the market could be expanded by using TPMT tests for other diseases where

thiopurine drugs are administered, such as rheumatoid arthritis, drug firms are not expected to be interested in promoting PGx tests.

The role of industry in ensuring that the tests reach clinical implementation was highlighted. A push by industry was the key to introduction of HER2 testing, whereas TPMT testing, being less commercially attractive, had no support from industry.

The pharmaceutical industry's interest in PGx seems limited to large markets: it has pushed HER2 and Herceptin in Germany and the UK, but has been more passive on the Dutch and Irish markets. It has expressed no interest in PGx for TPMT.

- Level of use varies highly between countries with different clinical protocols and acceptance levels. In most hospitals in Germany, Ireland and the Netherlands immunohistochemical HER2 testing is an integral part of a set of laboratory tests on breast tumour tissues. The outcome of the tests, together with other data (such as size and position of the tumour), forms the basis for an informed decision on the therapy to be used. The test can also be used as a means to forecast the probable development of the cancer. In the UK only 35% of cancer centres routinely test for HER2 status in breast cancer diagnosis. However, Herceptin is not widely used, for several reasons, and the protocols also differ. TPMT testing in children with ALL is not obligatory and, as a result, the frequency of TPMT testing differs between the four countries. In the Netherlands and Germany testing is conducted only when deficiency is expected. In the UK and Ireland almost all children are tested, but this is within a research project. It is not clear whether this will be the case after the research project finishes in 2007.

Level of use of testing also depends on the accepted clinical protocol, which is not the same across countries.

- PGx may be an addition to medical practice but is not necessarily going to replace existing tools. As shown in the TPMT case study, TPMT testing does not offer a complete solution to adverse reactions to thiopurine drugs. It must be used in addition to existing procedures rather than replace them. PGx is expected to mark an evolution, rather than a revolution in clinical practice.

PGx: an evolution rather than a revolution in medical practice

- Clinical practices are subject to financial constraints. Consequently, the availability of reimbursement for tests can be a crucial driver for the implementation of diagnostic technologies. In the Netherlands local hospitals have to make case-by-case decisions and the uncertainty of reimbursement is perceived as a definite barrier. On the contrary, in Ireland most PGx tests are reimbursed without issue due to the small scale of activities at present. In Germany reimbursement is available for procedures that are not explicitly barred from reimbursement by the Gemeinsamer Bundesausschuss. In the UK reimbursement decisions are made at hospital level, although in cases where there is regional variation the NICE may issue guidance (as occurred in the case of Herceptin and HER2 testing). In the USA reimbursement of a procedure under the federally funded Medicare and Medicaid programmes can be seen as an endorsement by private insurers. However, there are few national schemes to ensure that this is a smooth process. In the USA, PGx laboratories have to undergo time-consuming correspondence with local insurers to obtain reimbursement for a new service, although they are paid eventually.

Unclear or difficult reimbursement procedures for the tests are another major barrier to clinical uptake.

- The important influence that patient support groups can have on the outcome was exemplified by the active role patients' organisations have played and continue to play in the introduction of Herceptin as doctors still do not fully inform patients about all possible treatments. In all four countries breast cancer patients are informed that a number of tests will be run on their tumour tissue, but HER2 testing is not specifically addressed before the results become available. However, breast cancer patients are increasingly informing themselves through the internet and patients' organisations and ask their doctor about the test.

Patient groups can also influence clinical uptake by increasing awareness amongst their members who then request the treatment/test, thereby increasing use.

- Lack of education and training appears to be a strong barrier to implementation. There is little formal training or guidance for doctors and other medical staff on how to interpret PGx test results and only informal mechanisms to ensure that they understand the interpretation sufficiently. As a result, medical staff often depend on laboratories to supply information on how to interpret the results. However, this is the case not only for TPMT testing, but also for pharmacogenetic testing in general. The need for greater education on PGx for medical professionals is widely recognised. However, this is seen as a great challenge. It has been suggested that in the USA it will take a decade to train a new generation of practitioners in PGx. There is much competition for time in medical curricula and even at the leading US centres as little as 90 minutes is given over to such training. The UK case study revealed that not just specialist physicians require training but also nurses and junior doctors, as they too are often required to follow PGx protocols and this is expected to increase in future. The need for further training is also acknowledged in the German and Irish studies, although German physicians already complain about having too much new information to absorb. The UK case study in turn revealed that education in itself is not necessarily sufficient to guarantee the uptake of PGx, as the perceived relevance of tests varies between specialisms, depending on the frequency with which clinicians use particular drugs and are exposed to cases of adverse events. In Germany PGx is not considered relevant by some physicians who see the complexity of phenotypic and genotypic interactions as being beyond accurate prediction using a single testing methodology.
- Effective use of PGx tests in the clinic depends on the take-up of available services by the clinical community and accurate communication of the information supplied. In the USA, the UK and Ireland medico-legal responsibility for interpreting the results of tests ultimately rests with the clinical medical professionals or the institution that employs them rather than the laboratory staff. In the UK and Ireland concern was expressed that physicians could be legally liable in cases where patients did not receive the appropriate advice (for instance, if the clinician did not ask for the test to be performed). Despite these concerns, uptake of PGx tests is often poor, even with drugs such as thiopurines where ADRs are potentially fatal. In part this can be attributed to the lack of guidelines from professional bodies for PGx tests in general (although some tests such as HER2 have received more attention). However, even where guidelines exist, laboratory staff in the UK highlight that compliance is often a problem.
- Flow of information: Even where tests are requested, communication between the laboratory and users is sometimes poor, as highlighted in the German case study. Staff

in the UK laboratory are also concerned that many of their users are not fully grasping the utility of PGx tests. In such cases supporting mechanisms have been helpful. For example, the UK has recently established local cancer networks where pathologists and physicians regularly meet and can discuss the implications of test results. However, reporting requirements differ greatly between disciplines, for example a haematologist might expect less interpretation from a haematology laboratory than a clinical geneticist would expect from a clinical genetics laboratory.

- The problem of educating users is a central focus in PGx meetings in the USA. There are training courses for physicians although these appear to focus on a small number of disciplines. Conference presentations are used by laboratory staff in the UK to attract new users, although there are suggestions that education of users is difficult in a climate where over-promotion of the laboratory service itself is frowned upon.

One very big barrier to implementation is the lack of formal training and education. Introduction of a PGx test requires education of a wide range of medical staff; they have to learn to use and interpret the tests correctly.

- Societal issues do not pose a problem. Up until now, no problems have been perceived by physicians in asking for informed consent for a TPMT test. Nonetheless, the possibility of specific novel ethical concerns emerging in the future about particular PGx tests cannot be excluded.

PGx tests, whether based on DNA analysis or other methods, could reveal the presence of genetic changes which have implications for the patient beyond the therapeutic question initially addressed. For example, they could reveal information relevant to the patient's treatment with drugs that may be offered in the future, or reveal a risk of further diseases or a likely prognosis for an existing condition. They could also reveal information relevant to the medical care of family members.

Furthermore, like other types of clinical diagnostics, PGx test results cannot always predict the patient's drug response – environmental factors often play a role too – and therefore cannot be regarded as providing a definitive answer.

The views expressed in the case studies reported here seem to support the conclusions in the Nuffield Council of Bioethics report. In the USA, the UK, Germany, the Netherlands and Ireland, PGx tests have not been seen as ethically problematic by those working in the field although the extent to which clinical scientists have engaged in ethical debate is unclear. Certainly in the USA the field is seen to be too new for all the possible implications of testing to have been realised. In the future some PGx tests might possibly need to be accompanied by genetic counselling, as is required for some tests for genetic disease, but this will need to be decided case by case.

On the related issue of informed consent and PGx, the case studies suggest that even basic discussion with patients to obtain informed consent for PGx tests is often lacking, although this is a problem in other areas of diagnostic medicine and not unique to PGx.

Use of PGx in the clinical setting is too recent for the possible ethical implications to have been fully realised. New ethical guidelines are likely to be needed, particularly where test results have implications for immediate family members who might share similar genotypes with the individual tested.

Liability issues: As patients' knowledge increases, physicians might be sued for not testing patients in the event of severe toxicity. Liability concerns could therefore become a driver for PGx testing.

Cost-effectiveness analysis

Pharmacogenomic treatment strategies offer the potential to improve drug effectiveness,

reduce adverse drug reactions and provide cost-effective care. However, pharmacogenomics has had little impact on clinical practice. This could be due to medical, social, ethical and financial barriers. Information on the cost and effects of pharmacogenomic treatment strategies provided by cost-effectiveness analyses could (partly) level these barriers.

- Although an increasing number of applications of pharmacogenomics are described in literature, the economic implications are less often studied. In a recent systematic review of cost-effectiveness analyses of pharmacogenomic interventions Phillips & Van Bebber [1] identified only 11 studies that met the inclusion criteria for a cost-effectiveness analysis.
- For both HER2 and TPMT testing, an exploratory cost-effectiveness review was performed by developing models for comparing the costs and effects of the pharmacogenomic treatment strategy with current medical practice. For the four participating countries (Germany, Ireland, the United Kingdom and the Netherlands), information on model parameters was collected from literature and experts. The models established that both tests are cost-effective. TPMT testing could lead to financial savings and a gain in life-years. The analysis of HER2 testing in women with metastatic breast cancer shows that use of the FISH test to confirm all positive IHC results and use of the FISH test alone are efficient strategies. The aim of this exploratory cost-effectiveness exercise went beyond providing information on the expected cost-effectiveness of HER2 testing in women with metastatic breast cancer and TPMT testing in children with ALL and attempted to identify the parameters that need to be estimated more accurately to give a more definitive estimate of the cost-effectiveness of these two pharmacogenomic strategies. Another objective was to assess the feasibility of this type of studies in the EU. This kind of exploratory study combining evidence available from literature with expert opinions is useful for prioritising cost-effectiveness research on pharmacogenomic strategies and identifying which model parameters should be included in further research on the cost-effectiveness of this pharmacogenomic strategy, preferably in a prospective study using standardised methods.

Research on the cost-effectiveness of PGx testing in the clinical setting is scarce. Although this study has shown that both HER2 and TMPT testing are cost-effective, further research is needed for expert decisions on the use of PGx testing for many currently marketed drugs.

Clinical validity and utility

The findings agree across the case study countries that the evidence base is underdeveloped for many areas where PGx could be applied. To confirm the clinical validity of genotype-phenotype associations, detailed research is required. Furthermore, before a test can be widely used it must perform adequately in the population at large, including diverse ethnic groups, and detect a sufficiently full range of genetic changes occurring in the population. The heterogeneity of populations and more complex aetiology of many phenomena, such as adverse drug reactions, mean that at present clinical guidance is not available even for use in tests involving CYP450 and TPMT where clinically important genotype-phenotype associations have been recognised for many years. There is also growing acceptance that genetics will not explain the full set of causes of variability in drug response. Some commentators/respondents in the UK, Germany and Ireland are therefore now suggesting that PGx is likely to become an additional tool for clinicians rather than a technology which completely replaces existing approaches.

Choice of one or other of the cases might have drawbacks for generalisation. TPMT might not be fully comparable to other PGx tests. TPMT testing

in children with ALL seems to have low priority for physicians. However, this is likely to be because of the specific nature of the disease and treatment. In this disease TPMT testing does not offer a complete solution to adverse reactions related to thiopurine drugs. It must be used in addition to existing procedures rather than replacing them. However, the perceived utility of TPMT testing might be different in other patient groups, such as rheumatoid arthritis. Therefore, only to a certain extent can TPMT testing in children with ALL be seen as a model example of pharmacogenomic testing in practice. More research is needed.

Regulation of PGx products

Interviews were also conducted for comparative analyses of the regulatory and quality assurance frameworks in the USA, the EU and four EU Member States (Germany, Ireland, the Netherlands and the UK). In each country at least five, and in some cases more than ten, interviews were conducted.

Although it was shown that there was a strong technological push towards PGx activities, the regulatory impetus should not be neglected. The development of PGx expertise at the EMEA and FDA appears to have been spurred by industrial enquiries. This has led to pressure to develop new capabilities at regulatory agencies issuing licences for the US, EU and other markets.

The FDA's approach to capacity-building in the area of PGx is perceived by industry as being robust. Measures taken include the establishment of an interdisciplinary pharmacogenomic review group and joint workshops with industry.

In Europe the national agencies in Ireland, the Netherlands, the UK and Germany have received little demand directly from sponsors in relation to PGx. Indeed it appears to be more by accident than by design that the PGx products emerging at present correspond to those therapeutic areas where submission to the European centralised licensing procedure is already mandatory. PGx products are therefore being channelled through the EMEA. The EMEA draws on national agencies for its own expertise. Consequently, the lack of capability-building at national agencies could signal a need to bolster the EMEA's pool of expertise as the importance of PGx grows. So far the EMEA has been able to draw on academics and drug regulators for its PGx-related activities.

The EMEA began focusing on PGx in 2000, using workshops with stakeholders to address emerging needs. In 2002 an expert group on PGx was established, the first to be set up by any agency. This expert group on PGx includes academic and regulatory experts to advise on the approval of PGx-related therapeutics. The EMEA will expand its expertise to allow comprehensive assessment of PGx diagnostics in the development of drugs. However, the EMEA's licensing remit is not expected to be expanded to the approval of PGx diagnostics as products in their own right.

The EMEA has made internal appointments to aid its understanding of PGx and to facilitate further communication with the relevant scientific communities. Such internal appointments are important because assessors are external to the EMEA, and so information on PGx has to be digested within the Agency before it can be passed to the assessors as guidance.

As stated by respondents from industry, the activities of the FDA were an important signal to initiate and integrate PGx research into the companies' strategic research planning. At present companies seem happy with the final "Guidance for Industry Pharmacogenomics Data Submission" published by the FDA in March 2005. European companies hope that the EMEA will follow the US guidelines, as clarity from the regulatory agency on what is needed is crucial for advancing PGx.

Industry seems to view the FDA's approach to PGx as more pro-active than the EMEA's approach.

The issue of harmonisation between jurisdictions in relation to PGx regulatory policies is important. Evidence from this study suggests that there appears to be general support for greater harmonisation in industry. However, industry is undecided about the time-scale over

which this might be achieved. Some respondents from industry were sceptical about whether harmonisation could be achieved; others were keen that it should be achieved and disappointed with progress to date, while others felt that harmonisation should not be aimed for too quickly in a field that is changing rapidly to avoid making future regulatory changes more difficult.

Lack of harmonisation of regulations related to PGx testing across the EU is perceived as a possible barrier, but pharma are undecided about the urgency of the need to achieve harmonisation.

Use of PGx data in licensing decisions

It is clear from the evidence gathered in this study that almost all clinical trials carried out by large pharma now involve gathering genetic data, although this is not required for regulatory submission purposes. The FDA responded to the challenge of use of PGx data in clinical trials with its voluntary genomic data submission programme and a series of draft guidance documents, culminating in March 2005 with final release of the pharmacogenetic guidance.[134] An FDA concept paper was also recently produced on drug-diagnostic co-development.[135] Since these two sets of FDA documents were only recently released, it is too early to provide a detailed review of how they have been received although, as reported in Chapter 4, the FDA approach has been broadly welcomed by industry. However, challenges remain, notably on the validation of biomarkers, with the FDA favouring a more conservative view of what constitutes a probable as opposed to an exploratory biomarker.

In 2002 the EMEA began to discuss the use of genetic data with sponsors by holding one-to-one briefing meetings outside the regulatory process. Briefing meetings are a strategy used by the EMEA in a number of areas beyond PGx. The EMEA hopes to provide further support for sponsors in the future. There are no definite plans as yet about compulsory submission of PGx data by the EMEA.

The industry's view of the EMEA's approach has been less favourable, and there is a perception that the EMEA is "lagging behind", while the FDA has been more engaged with industry and is thought to be more transparent.

The national agencies in the Netherlands and Ireland have not yet been approached with requests to consider PGx data and are following a "watch and wait" approach. In the UK there are no plans for the MHRA to require PGx data from clinical trials in the near future, although such information would be considered as part of the MAA process if it were submitted.

Licensing of PGx products: drug-test combination or separate approval?

The licensing of therapeutics in combination with a diagnostic test was seen as presenting significant challenges for the FDA as it blurs the boundaries between the centres that traditionally handle the different areas. A new Office for Combination Products was established in 2002 to address some of the emerging issues by taking the lead in combination product applications (PGx being only one area where such products are emerging – others include vascular stents that release drugs over time). It is too early to say whether these measures have substantially addressed consistency, transparency and internal communication in the process –issues that had caused some concern. Also there is the question whether PGx-based products will inevitably be defined as "combination products" under US law. The FDA OCP is expected to take on a coordinating role with such products, mediating between the different FDA Centers.

134 http://www.fda.gov/cber/gdlns/pharmdtasub.pdf accessed on 1.6.2005.
135 http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed on 1.6.2005.

Ireland, the UK and the Netherlands already follow a single-agency approach with drugs and devices licensed by the same agency while Germany still has separate institutions. Beyond the case studies Germany's position seems to be the more common, as comparatively few countries have taken the single-agency approach, according to the EMEA source interviewed in this study.

In the EU, the EMEA does not approve diagnostic and therapeutic combinations as the Agency does not have primary responsibility for diagnostics and its remit is limited to approval of therapeutics. The EMEA is not seeking an extension of its mandate to cover diagnostics and its present remit is not seen as presenting a barrier to the approval of such PGx diagnostics products.

The procedure for separate application to the national agencies for the diagnostic elements of PGx products is set to continue, with improved channels of communication between national diagnostic authorities and the EMEA expected to be developed for consultation where appropriate.

At present, regulatory agencies have limited experience of dealing with PGx products due to the small number of PGx products that have emerged to date. Those that have been produced have not been co-developed to the degree that may be seen in the future. Indeed Ireland's agency reported that it had no significant experience with PGx products to date. In the UK, Germany and the Netherlands, cases like the approval of the HER2 kit in conjunction with the centralised EMEA approval of Herceptin are reported to have posed some challenges, but were nonetheless accomplished satisfactorily. However, these systems are relatively untested at present as most genome-based drugs are only now moving into development. Furthermore, there are concerns about whether the present provisions in the EU are sufficient for PGx diagnostics.

The IVD Directive sets out a common regulatory process for diagnostic devices in the EU which include the test component of a PGx drug and test combination. However, the EMEA is concerned that the CE mark is granted solely on the basis of technical accuracy and not of clinical utility, although apparently this has not raised concerns with the regulators such as the UK's MHRA. Nonetheless this is important as the evidence supporting clinical utility is regarded as one of the main challenges facing PGx.

At present the EMEA can recommend the use of a diagnostic test as part of the labelling process (see below). However, it is not clear how diagnostic use could be enforced in Member States or how non-marketed tests, such as those developed in hospital laboratories and outside the scope of the IVD Directive, could be regulated. Clearly these issues, including the question of clinical utility, are also relevant to the regulation of genetic tests unrelated to PGx and to other kinds of diagnostics.

Experience with co-development of a drug and a PGx diagnostic test is limited, making it impossible to draw conclusions about its feasibility and novel regulatory needs.

Labelling of new medicines with PGx information and re-labelling of old products to include new PGx information

To date there are few examples in the EU of new products requiring labelling to accommodate PGx data. When such information about PGx testing is required, there is no standard way of presenting it on the drug's label or data sheet. Consequently, the inclusion of PGx information in a drug MA is handled on a case-by-case basis. The EMEA has been able to label drugs, such as Herceptin, with instructions in the MA that the product be used only after an appropriate diagnostic test has indicated the patient has the susceptible type of tumour.

The FDA is also presently handling the need to include PGx data on the drug label on a case-by-case basis and has also been able to require that a diagnostic be used with a drug.

Where new clinical data emerge which suggest a PGx diagnostic would significantly improve the safety of a drug already available on the market, there is a legal mechanism (Article 31) that allows the EMEA to recommend a change of labelling to Member States. However, this has not yet been applied for PGx. Similarly, the FDA has powers to revise drug labelling as new data emerge, and has already issued new advice on the basis of PGx data for the cancer drug irinotecan, although mandatory PGx testing has not yet been applied to a product already on the market.

In any situation where new data on a licensed drug emerge, regulators have emphasised the need to address scientific uncertainties carefully and their duty to act only on robust data.

Market segmentation and orphan drug status

Previous reviews of PGx suggest that the segmentation of markets due to genotypic differences associated with drug response is a cause for concern because it is thought that development of treatments for conditions affecting smaller genetic groups will be unattractive for drug developers. This concern is shared by agencies such as the UK MHRA, which suggests incentives may be needed to improve availability of therapeutics for some groups of patients. In the USA sponsors have the options of both accelerated "unmet medical need" approval schemes and orphan drug provisions. As such the FDA view is that the frameworks are in place to ensure that such a situation would not be a major challenge. Herceptin was granted the status of an orphan medicine for the subset of pancreatic cancers that overexpress HER2. Medicines are most commonly denied orphan medicine status because of disagreements over how target populations are defined. Although in many cases rejections might be justified to prevent drug companies from dividing markets in a creative way, these cases nevertheless suggest that the seemingly academic issue of reclassification of disease through pharmacogenetic analysis might have significant implications for regulatory frameworks. Legislation on orphan drugs exists in Germany and the Netherlands, but not in the UK or Ireland. European provisions on orphan drugs remain untested for PGx products.

The EMEA draws a distinction between market segmentation that divides patients according to response, for example due to variations in metabolic activity, and segmentation which divides diseases by aetiology. While drugs in the latter category have been licensed for cancer, the EMEA has not been faced with any examples of the former and would wish to avoid making such a licensing decision unless this was the only viable option.

Orphan medicine status, allowing an accelerated drug review process, may create an incentive for pharma to develop drugs for small patient sub-populations based on PGx testing. However, too few examples exist for drawing conclusions on the need to revise orphan medicine regulations in the EU.

Regulation of PGx testing in the clinic

There are very few examples in the USA or EU of PGx tests that are used on a large scale. Perhaps the most widely used is HER2 testing, with the number of laboratories testing for overexpression of HER2 estimated as running into hundreds in both the USA and EU. Given the similarity in methods for detection of other cancer-related biomarkers, it seems that oncology is one area where significant PGx testing will continue to develop.

Those tests that have been developed are being used in a wide range of public- and private-sector laboratories. While it is technically possible for point-of-care tests to allow PGx testing by pharmacists or physicians, at present there is no evidence of this. This analysis assumes that such tests will continue to be conducted by laboratory staff in the near term. Laboratories conducting PGx testing have staff from a range of scientific disciplines, such as molecular genetics, clinical

chemistry and histopathology. The range of tests offered and workload received vary substantially and in some cases research laboratories rather than dedicated clinical laboratories provide services. This raises concern about the provision of services offering adequate quality and reliability. Satisfactory implementation of PGx testing will therefore depend on the prompt uptake of new diagnostic technologies by clinical laboratories for further assessment to reduce the number of such services provided by research laboratories.

Factors found to influence test availability and quality in the case study countries include laboratory licensing, laboratory accreditation, external QA schemes (also known as ring testing or proficiency testing) and financial reimbursement controls. These are explored in more detail below. Once the clinical applications of PGx grow substantially in future years, support for these systems will increase and become more important. This pattern of development has been seen in a number of laboratory disciplines in recent years, including testing for genetic diseases.

- Licensing of clinical laboratories - The countries studied vary widely with regard to licensing laboratories providing clinical testing services, whether for PGx or more generally. In the USA and Germany laboratories are required by law to have a licence to operate. In the USA for example, even research laboratories are discouraged from reporting test results unless they are CLIA-certified. In Ireland, the Netherlands and the UK there are no licensing systems and, at least in principle, any laboratory can offer the service. None of the countries studied has special licensing for genetic testing, although a new set of CLIA rules for genetic testing is being developed in the USA.
- Accreditation of clinical laboratories - Accreditation schemes aim to provide an independent inspection system that reviews laboratory staff performance, infrastructure and processes to maintain service quality. These schemes are generally based on international quality standards such as ISO 9001. Laboratory accreditation schemes have been established in the USA, Germany, the Netherlands, the UK and Ireland. However, smaller countries often lack a sufficient scale of activity to run accreditation schemes in all disciplines. Irish laboratories, for instance, often join a UK scheme. These schemes are run by private professional bodies, often affiliated to the national pathology community. In countries like the UK and the USA a proliferation of schemes offers some choice. In the USA the scheme is tailored to different disciplines, such as molecular genetics, which is also the approach being developed in Germany. In practice one problem with the accreditation system is that membership of schemes is often not mandatory, or where it is encouraged, is not enforced. For example, in the UK laboratories are increasingly encouraged to join accreditation schemes, but some cannot pass the inspection process due to infrastructure deficiencies that they cannot address because of financial constraints. However, the impact on local services if these were to be closed down would be too severe for such action to be contemplated.
- External QA schemes - External QA schemes encourage improvement of testing quality by revealing and disseminating best practice. As such they are generally welcomed by participants. Such schemes identify laboratories that are performing poorly and provide them with assistance. As previously mentioned, QA schemes are not sufficiently developed in the USA and the EU in the area of genetic testing as a whole.[136] Unsurprisingly there are few dedicated PGx schemes as yet, although HER2 schemes are well established in the EU and USA, and a global TPMT testing scheme is being piloted by a UK laboratory.

136 IPTS (2003) "Towards quality assurance and harmonisation of genetic testing services in the EU", IPTS, Seville; OECD (2005) Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Survey of 18 OECD Member Countries, Paris: OECD.

This illustrates the increasing trend towards international QA schemes. International schemes are of particular benefit to small countries which perhaps lack the "critical mass" to launch a national scheme. Support for international QA schemes could therefore be a major priority for the EU in the field of PGx. One point to note is that the existing QA schemes for PGx are not linked to previously established schemes in other areas of genetic testing. Building such links would be of benefit for cross-fertilisation of ideas and could reduce duplication of effort. Poor performance in a QA scheme is sufficient for a UK laboratory to lose its accreditation and for a US laboratory to have its CLIA certification revoked for the assay under consideration. However, many laboratories, particularly research laboratories, do not sign up to these schemes. Only in the USA is membership of such schemes linked to licensing, thus ensuring higher participation rates. The inability to impose sanctions on poor performers frustrates some organisers. Some German clinical laboratories and UK research laboratories have suggested QA schemes are excessively time-consuming. Continued growth of QA schemes could therefore require greater support for some laboratories to enable them to participate.

Quality control of the tests is also very different. Use of approved and labelled test kits, such as the one produced by DakoCytomation, is not enforced in any of the countries studied. The QA scheme "regulates" the use of PGx tests in the four countries. Accreditation systems are in place (in most cases on a voluntary basis) in commercial laboratories, but not in most hospital laboratories. It is widely recognised that the more experience with the test, the better the guarantee of quality. Therefore, the number of tests conducted is considered a reliable quality indicator. According to Roche, 150 tests a year is a minimum. In the UK guidelines have been introduced that require an annual caseload of at least 250 cases. Irish laboratories that perform HER2 testing participate in the UK's QA scheme. The Netherlands operates a system where colleagues assess each others' tests and develop quality standards. QA schemes and performing a high volume of tests each year are two readily available options to achieve higher quality laboratory testing. Due to the high cost of commercial tests, hospital laboratories have developed their own "home brew" tests. Producers of commercial test kits, as well as some laboratory staff, call into question the quality of some of these home brews.

Quality assurance (QA) for PGx testing in the EU, like other diagnostics, differs across Member States and participation in QA schemes is only voluntary in most of them. There are concerns about the quality of non-commercial tests, especially when performed in smaller hospitals with less experience.

Validation of new PGx tests in clinical laboratories and use of "home brews"

Before a PGx test is provided as part of routine clinical practice it is desirable to examine a number of factors that will affect its clinical performance. These include the test's technical accuracy (i.e. that the test performs reliably technically with false positives or false negatives kept to acceptable levels), clinical validity (i.e. that the marker detected is clearly linked to a clinically relevant condition or status) and the prevalence of variation in population (i.e. that the test will be reliable in the laboratory's target population). These factors and their implications for specific PGx tests have been reviewed in more detail elsewhere [61]. However, as mentioned above, there are no mandatory controls in the EU that influence the introduction in hospital laboratories of PGx tests developed in the public sector. Indeed under the EC's IVD Directive hospital laboratories have been granted exemptions from conditions applying to providers in the private sector. This has caused some concern in the diagnostics industry, which suggests that firms providing the same services as hospital laboratories will be

regulated more heavily. Nonetheless in countries such as the UK, where the NHS relies heavily on hospital laboratories, a stricter regime would have a significant impact on the cost of healthcare provision. The situation is slightly different in the USA. There non-commercial laboratories are free to develop "home brew" kits without approval from the FDA. However, in order to maintain CLIA certification for that service they must demonstrate that they have taken a series of steps to validate the test before it is introduced. Under the CPA scheme UK laboratories are also advised to validate new services, but in both cases it appears some users feel this process is rather weak.

This diversity of laboratories brings with it a diversity of approaches to conducting the same PGx test, as might be expected in an emerging field where practitioners are often close to the science base. A close network of formal and informal links between laboratories can often be instrumental in reducing variability in performance and spreading good practice. Well-developed systems for peer inspection and benchmarking such as external QA schemes exist in all the countries studied, although schemes for some PGx tests have yet to emerge, and those that are active have not been given sufficient powers to prevent poor performers from continuing to offer services.

The diversity of laboratories engaged in PGx testing means that often no single national professional network, body or institution is able to oversee the activities of the community as a whole. In some cases, such as HER2 testing, different methodologies might be promoted by different communities and cross-disciplinary initiatives are needed to bring key individuals together to inform best practice.

One approach often associated with standardisation is the availability of a commercial kit. However, in practice this is not always the case. It is certainly true that commercial kits in the USA and EU are subject to greater quality control regulation than "home brew" kits developed within test laboratories. However, the cost differential between the price which laboratories must pay for these kits and the price they pay for the constituent elements provides a strong incentive for laboratories to find ways of manufacturing their own kits or modifying existing ones. This is occurring with HER2 kits, but is not confined to PGx. The cost of commercial kits has been cited as a specific factor preventing standardisation in the UK, the USA and Germany.

Broader use of commercial PGx testing could circumvent some of the problems associated with quality assurance and wider implementation. However, the costs of such kits and reimbursement issues are currently a major barrier.

A range of expectations surround the potential impact of PGx. The extent to which PGx is seen as having the potential to provide significant benefits in R&D and medical practice appears to be proportionate to the efforts put into its implementation. Of the countries studied, the USA has provided the broadest support for PGx, with enthusiastic policy support in the form of generous NIH funding and well coordinated multi-stakeholder lobbying. However, those at the forefront of clinical research see developments as taking longer to bear fruit than initially anticipated. In the UK, policy support is also evident although the sums invested are modest. The response of clinical researchers in the UK to PGx has been more cautious than in the USA, based on the assumption that it will be of marginal utility rather than a revolution in medicine. The view at the policy level in the UK suggests that little clinical impact can be expected in the short to medium term. In the Netherlands PGx has not been a focus of attention at policy level although there has been enthusiasm about the potential impact on therapeutic R&D. However, industry is expected to be the main driver of change. In Ireland there has been little direct policy focus on PGx, although national programmes for genetic research exist and there are high expectations for PGx in the research community. In Germany PGx has not received attention at the policy level and no specific expectations have been reported.

Support for PGx, in terms of both policy and dedicated funding, is stronger in the USA than in the EU. Among the four Member States surveyed, government support for PGx is strongest in the UK, but even there it does not approach the US levels.

In summary, PGx technologies have the potential to improve both drug safety and drug efficacy, two crucial aspects of pharmacotherapy where improvements are needed. This could allow substantial healthcare savings. However, introduction of PGx in the clinical setting is seen by many US and European experts as slower than expected due to several barriers. As outlined in this IPTS report which examined the situation in four Member States, the **key barriers** in the EU include:

- Lack of earmarked funding programmes in the EU modeled on the US NIH Pharmacogenetics Research Network (PGRN) and for industry-academia collaboration;
- Lack of incentives for developing diagnostics to improve the safety and efficacy of current drugs by re-licensing along with a PGx diagnostic;
- Lack of cost-effectiveness studies on the application of PGx;
- Lack of formal PGx education for healthcare professionals;
- Lack of harmonisation of regulations related to diagnostics and to drug/test co-development;
- Lack of clear reimbursement procedures for PGx diagnostics;
- Lack of a clear understanding and agreement on harmonised ethical guidelines and national practices regarding the collection and storage of PGx data and on DNA banking and biobank access.

In this context, additional policy actions might be needed to address these barriers so that PGx can deliver its potential for safer and more efficacious medicines.

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Annex 1: summary of research methods

We used diverse methods including a range of publication and commercial database search strategies, online surveys, policy literature reviews and in-depth interviews as the basis for our findings. The project consisted of three streams of research and relied on a range of methods to gain quantitative and qualitative data. In particular a large number of semi-structured interviews were conducted with representatives of prominent institutions involved in PGx in the countries studied. Please note many interviewees contributed to more than one stream.

Mapping R&D activity in pharmacogenetics and pharmacogenomics.

A key aim was the identification ofnoncommercial research institutions (e.g., hospitals, charities, universities) in the United States, Europe and Japan. Results are based on manual and keyword searches of academic literature in conference proceedings, journals, online databases and the web. This search revealed 264 relevant institutions. The 264 institutions were surveyed using an online questionnaire to explore issues such as areas of research interest, funding and collaborative activities. Sixty responses were received overall (23% response rate). Identifying commercial groups with significant R&D programs relating to PGx was another key aim. Using industry databases (http://www.gendatabaseonline.com/, http://www.marketresearch.com/, http://www.newsanalyzer.com/, http://www.recap.com/) a universe of over 1,000 companies was searched to identify companies with a focus on PGx. Companies were profiled on the basis of public documents such as press releases and SEC filings. Interviews with 20 prominent academic departments and companies were conducted to provide more detailed insights into the themes emerging from the survey. Interviewee selection was guided by information from the literature and website searches to capture a broad range of experience–for example, United States versus EU, diagnostic development versus drug development.

Case studies on the application of PGx tests in the clinic in four EU countries.

Using a common research design, qualitative case studies were undertaken by researchers in Germany, Ireland, the Netherlands and the UK. Case studies were based on a review of academic literature and policy documents, as well as interviews with clinicians, laboratory staff, industry, government healthcare policy makers and health insurers. Interview themes were guided in part by a pilot survey sent to 407 physicians in four countries, the results of which are reported elsewhere18. Two PGx applications were chosen: testing to improve drug efficacy (HER2 testing) and testing to improve drug safety (TPMT testing).

HER2 expression testing before prescription of Herceptin in treatment of late-stage breast cancer.

The number of interviews conducted in each country was as follows: Germany, 18; Ireland, 11; the Netherlands, 11; the United Kingdom, 36.

TPMT activity testing before prescription of 6-mecaptopurine in treatment of acute lymphatic leukemia.

The number of interviews conducted in each country was as follows: Germany, 21; Ireland,

11; the Netherlands, 7; the United Kingdom, 11.

Case studies on regulatory frameworks influencing PGx use.

Using a common research design, qualitative case studies were undertaken to describe the regulatory environments for PGx in the United States, Germany, Ireland, The Netherlands and the UK, as well as relevant EU-wide frameworks. A broad interpretation of regulation was applied, spanning factors that shape the effective use of medical technologies from the bench to the clinic (for example, the development/licensing of drugs and diagnostic tests, oversight of testing services and availability of clinician education/guidelines). Data collection focused on reviews of the academic and policy literature, interviews with regulatory authorities (including the EMEA and FDA), quality assurance scheme administrators and laboratory staff). Interviews with 15 companies chosen as described above to provide additional insight also informed this stream of activities. The number of interviews conducted in country was as follows: US, 11; Germany, 21; Ireland, 16; the Netherlands, 5; the United Kingdom, 9.

PGx companies were identified according to the methodology described in section 1.1.3. The alliances were identified from www.recap.com only. All listed alliances and patents are specific to PGx. The number of patents refers only to US PTO granted patents.

Name and location	Age and size			Technology and business strategy			
Name Web site Country	Started Public/ private	No. staff R&D spend p.a.	No. alliance.	No. Patents	Involvement in PGx	PGx-related services (technical option)	PGx-related products (technical option)
Astex Technology www.astex-technology.com UK Mn64	1999 Private	-		?	Developing a programme of drug discovery and rescue based on Cytochrome (CYP) P450 structures.	*Discovering new drugs that work well in entire population* – solving CYP p450 crystal structures to help optimise compound selection and design. *'Rescue' of products in later stage clinical trials (ADRs)* - data on CYP p450 crystal structures to help rescue products in development.	
deCODE / Encode www.decode.com Iceland	1996 Public	414 (2003) 63.5 m $ (2003)		3 Diagnostic applications of osteoporosis and narcolepsy genes	Identifying genetic causes of more than 50 common diseases. Expression profiling to identify clinical response profiles of drugs in development. Identifying genes that predict the responsiveness to drugs for common conditions.	*Later stage trial design and monitoring to target 'good responders'* – Clinical trial services and genotyping to identify and analyse good responders to a drug.	*Pre-prescription screening to identify 'good responders'*- developing diagnostic tests - with Roche to predict response of patients to asthma and hypertension drugs - with Affymetrix to identify responders/ non-responders to popular drugs.
Epidauros Biotechnologie AG www.epidauros.com Germany	1998 Private	26 (2003) 3.7 m $ (2002)		2 CYP variant and drug sensitivity gene	Investigating polymorphisms in ADME genes and have developed 70 pharmacogenetic assays based on these variants. Interested in working on drug candidates that have previously failed Phase II and III clinical trials and aim to test pharmacogenetic hypotheses to find the cause of failure. Aim to 'rescue' drug and seek and approved for use along with a pharmacogenetic test.	*Pre-clinical testing and early stage trial design/monitoring* – Screening assays of ADME gene polymorphisms. *'Rescue' of products in later stage clinical trials (ADRs)* - Clinical studies for retrial of drug in population selected by genotype. *Later stage trial design and monitoring to target 'good responders'* – 'Good responder' patients selected for clinical trials based on genotype. *Drug rescue (Efficacy)* - Clinical studies for retrial of drug in population selected by genotype.	Discovering new drugs that work well in entire population – Development of PGx assays (ADME gene variants). Pre-clinical testing and early stage trial design/monitoring - MDR1 pharmacogenetic profiling assay, CYP3A and CYP2D6 pharmacogenetic profiling assay. 'Rescue' of products in later stage clinical trials (ADRs) - Predictive pharmacogenetic test for rescued drugs. Drug rescue (Efficacy) - Predictive pharmacogenetic test for rescued drugs.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Genset www.genset.fr/ France	(part of Serono)			11 Diagnostic markers and genes (arthritis, obesity, asthma, cancer, schizophrenia)	Identifying genetic factors that influence metabolism and the molecular target of drug action, and how they contribute to individual variability in drug response. Combinatorial analysis of genome-wide genetic and pharmacogenetic data.	No details available – in process of restructuring/ disinvestment	No details available - in process of restructuring/ disinvestment
Diagnostics only							
Axis-Shield www.axis-sheild.com UK/ Norway	1999 Public	440 (2003) 12.9 m £ (2003)		0	Develops diagnostic tests based on theranostics for therapeutic stratification and monitoring of drug response. Theranostics involves individual disease risk prediction and diagnosis, therapeutic stratification and monitoring of therapeutic response.		*Later stage clinical trial design and monitoring to target 'good responders'* - Diagnostic tests for patient stratification. *Pre-prescription screening to identify 'good responders'* – Diagnostic tests to target drug therapy at responsive sub-group. Diastat immunoassay for targeting rheumatoid arthritis drug. *Use of efficacy data in drug marketing* – extending product life cycle using stratified efficacy data.
Dakocytomation www.dakocytomation.com Denmark	1966	1300+ (2004)		-	Dakocytomation develop diagnostic tests to allow patient selection for specific cancer therapeutics. These tests are based upon the identification of an over-expressed protein in tumour cells.		*Stratification of diseases and infectious agents into sub-types* - Diagnostic tests to identify sub-populations of cancer patients who will benefit from a particular drug. ***HER2* FISH pharmDx test was developed for patient selection for treatment with Herceptin** (breast cancer). **EGFR pharmDx test is used to select patients for treatment with ERBITUX** (colorectal cancer). It is also in clinical trials to qualify cancer patients for treatment with the drug ICM-225.
Epigenomics AG www.epigenomics.com Germany	2000 Private	100 (2003)		0	Research focuses on analysis of DNA methylation patterns for use in cancer diagnostics. Discovering disease-specific biomarkers and develop pharmacogenetic tests to be used as a guide for prescribing drugs.	*Stratification of diseases and infectious diseases into sub-types* - Clinical genotyping, support services and association studies of efficacy for patient stratification.	*Pre-prescription screening to identify 'good responders'* - developing diagnostic tests. **With Roche have developed a pharmacodiagnostic test to predict the probability of relapse of patients treated with tamoxifen.** *Stratification of diseases and infectious agents into sub-types* - Pharmacogenetic tests to stratify patients into responder/ non-responder groups.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Ipsogen SAS www.ipsogen.com France	1999 Private	28 (2003)		0	Developing a range of diagnostic gene expression biochips for profiling breast cancer, lymphomas and colon cancer. Pharmacogenomic studies in oncology using focused patient recruitment.	*Later stage trial design and monitoring to target 'good responders'* – Gene expression analysis services to enable patient stratification in clinical trials.	*Stratification of diseases and infectious diseases into sub-types* - **Biochips for expression analysis to predict patient response to anti-cancer drugs**.
Jurilab www.jurilab.com Finland	1999 Private	35 (2004)		2 Gene variant linked to range of common disease. PGx kit.	Developing microarray-based tests for disease predisposition and drug response.		*Pre-clinical testing and early stage trial design/monitoring* - **Sells the DrugMEt DNA microarray test to detect SNP polymorphisms in panel of drug metabolising enzymes (CYP, TMPT, NAT2, MRD-1).** *Pre-prescription screening to identify 'good responders'* - **Developing predispositional genetic tests for CGD, hypertension, obesity and diabetes that will help guide prescribing e. g. HeartGEn CHD test**
LGC www.lgc.co.uk UK	1996	600 (2003)		0	They offer a pharmacogenetic diagnostics, genotyping, consultancy and research service. HyBeacon assays have been developed for use in point-of-care testing devices to guide prescribing.		*Pre-clinical testing and early stage trial design/monitoring* – **Screening assays of ADME gene polymorphisms**. *Pre-prescription screening to identify patients at risk of ADRs* – licensed CYP2D6 patent to number of firms. *Pre-prescription screening to identify 'good responders'* – **HyBeacon assays to identify good responders.**
TheraStrat www.therastrat.com Swizerland	2000 Private			0	Focus on supporting clinical development and post-marketing surveillance. Developing products to predict the molecular basis of severe ADRs. Aims to identify the susceptibility of individuals to ADRs and help pharmaceutical companies to eliminate drug candidates with severe ADR profiles.		*Pre-clinical testing and early stage trial design/ monitoring* – Database and development of chip-based assays to help eliminate drug candidates with serious ADRs. Commercialisation agreement with Discovery Partners, Inc. *'Rescue' of products in later stage clinical trials (ADRs)* – Database and development of chip-based assays to eliminate patients in trials at risk of serious ADRs. *Post-marketing surveillance* – Database and development of chip to identify patients at risk of serious ADRs.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Vita Genomics www.vitagenomics.com Taiwan	2001 Private	120 (2003)		0	Researching the genes and pathways involved in liver disease and the responsiveness of patients to drugs. Have identified genetic variation and developed tests to detect differential drug response to interferon alpha in Hepatitis B and C patients.	*Later stage trial design and monitoring to identify genomic sub-populations who are 'good responders'* - Clinical association studies and genotyping services. *Stratification of diseases and infectious agents into sub-types* - Clinical association studies and genotyping services to stratify infectious agents into genomic sub-types according to drug response.	*Pre-prescription screening to identify 'good responders'* – Developing pharmacogenetic tests for a range of common diseases. *Stratification of diseases and infectious agents into sub-types* - **Diagnostic tests to predict response to interferon alpha among Hepatitis B and C patients**.
PGx service firms							
The Brain Resource Company www.brainresource.com Australia	2002 Public	0.5 m $		-	Developed an internationally standardised database of the brain including information on the subjects medical history, electrical brain function, cognition, imaging of the brain and cognition. The database can be used to identify new markers for brain function and assess the impact of treatment on these markers. The NeuroMarker Profiling Toolkit is a computer-based tool for pharmacogenetic drug evaluation during clinical trials and for licensed drugs.	*Discovering new drugs that work well in entire population* - Application of NeuroMarker Toolkit for studies of toxicity. *Discovering new drugs aimed at genomic sub-populations* - Application of NeuroMarker Toolkit. *Pre-clinical testing and early stage trial design/ monitoring* - Application of NeuroMarker Toolkit *Later stage trial design and monitoring to target 'good responders'*- Application of NeuroMarker Toolkit.	
CXR www.cxrbiosciences.com UK	2001 Private	33 (2003)		0	Pharmacogenetic services for preclinical drug development. Researching the effects of cytochrome P450 in drug metabolism, response to drugs and adverse reactions to treatment using a transgenic mouse strain (HRN) with conditional deletion of the P450 reductase gene in liver tissue.	Discovering new drugs that work well in entire population – Use of HRN in drug metabolism and safety studies. Pre-clinical testing and early stage trial design/ monitoring – Use of HRN in drug metabolism and safety studies. *'Rescue' of products in late stage trials (ADRs)* – Their genetic techniques can be applied to rescue molecules with unexplained toxicological observations.	*Discovering new drugs that work well in entire populations* – **Assays of ADME variants and CYP450 profiling.** *Pre-clinical testing and early stage trial design/ monitoring* – **Assays of ADME variants and CYP450 profiling.**

Name and location	Age and size			Technology and business strategy			
Name Web site Country	**Started Public/ private**	**No. staff R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
DxS www.dxsgenotyping.com UK	2001 Private	13 (2003)		0	Provide pharmacogenetic services during drug discovery, development and marketing using Scorpions genotyping system and ARMS mutation detection technology. These are used to predict individual response to drugs and in the typing of infectious pathogens.	*Discovering new drugs that work well in entire populations* - Research genotyping to provide assays of common variants of drug metabolising genes (e. g. CYP etc.) *Pre-clinical testing and early stage trial design/ monitoring* – Genotyping of clinical trial population. *Later stage clinical trial design and monitoring to target 'good responders'* - SNP analysis to measure variation within the clinical trial population and aid the selection of patients.	Pre-prescription screening to identify 'good responders' – Developing test to predict response to ERFR-based anti-cancer drugs (e. g. Iressa).
Medigenomix www.medigenomix.de/en/ Germany	1998 Subsid of Eurofins Group			-	Medigenomix provide companies with pharmacogenetic services during drug development. Their technology involves screening for mutations in G-protein genes to predict responders/ non-responders to drugs and identify patients likely to suffer ADRs.	Pre-clinical testing and early stage trial design/ monitoring - Genotyping for variations in G-protein genes. Later stage clinical trial design and monitoring to target 'good responders' - Genotyping for variations in G-protein genes.	
PGx tools, kits and software firms							
Amersham Biosciences www4. amershambiosciences.com UK	1997 Public	9000 (2004) 184 m £ (2002)		2 Foetal abnormalities and mutation detection kit	Amersham Bioscience provides researchers with their CodeLink system, which can be used for gene expression profiling, SNP genotyping and pharmacogenetic profiling during drug discovery and development.		Pre-clinical testing and early stage trial design/ monitoring – CodeLink for SNP genotyping and pharmacogenetic profiling. Have p450 SNP Bioarray (i. e. CYP gene alleles)
Biotage (Pyrosequencing) www.biotagebio.com Sweden	2003 Public			0	Sells Pyrosequencing chip genotyping technology, which can provide functional assays for CYP450 mutations, and analyse and validate any other pharmacogenetic markers.		Pre-clinical testing and early stage trial design/ monitoring – Pytosequencing assays of CYP450 mutations.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
PGX Drug Development and Diagnostics							
Curagen http://www.curagen.com USA	1993 Public	327 (2003) 64.5 m $ (2003)		4 1) Treatment and diagnosis of cardiac hypertrophy; 2) diagnosis, prognosis and screening for a disposition for stroke; 3) predisposition towards stroke, hypertension, diabetes and obesity; 4) genetic diagnostic for thyroid cancer linking to appropriate treatment.	Predictive Toxicogenomic Screen used to assess the safety of new drug candidates and the safest candidates can be chosen for lead optimisation.	*Discovering new drugs aimed at genomic sub-populations* - Identify drug candidates that respond well in particular genotypes and alternative targets for drug development. *Preclinical testing and early stage trial design/ monitoring* – Use of Predictive Toxicogenomic Screen to perform pre-clinical safety studies.	*Discovering new drugs aimed at genomic sub-populations* – Libraries of drug candidates that respond well in particular genotypes.
Egeen International http://www.egeeninc.com/ USA	2001 Private	30+ (2004)		0	Conduct clinical trials on a fee for service basis. Aim to help develop PGx diagnostics to reformulate drugs facing patent expiry for more targeted treatment..	*Later-stage trial design and monitoring to target 'good responders* - Clinical association studies to complement clinical trials with pharmacogenetics. Patients are stratified into subgroups depending on response to drugs. Development of 'focused' clinical trials.	*Pre-prescription screening to identify 'good responders'* - **Studying PGx SSRIs (Paxil) and drugs for hypertension with Prediction Sciences.** Working towards the development of predictive diagnostic tests. *Use of efficacy data in drug marketing and in extending patent life* – aims to develop tests to enable reformulation and patent extension.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. alliance.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Genaissance Pharmaceuticals Inc. www.genaissance.com USA	1997 Public	200 (2004) 20.1 m $ (2003)		4 1) Genetic typing of the human cytochrome P450 2A6 gene (smoking, asthma); 2 &3) Variation in drug response related to lymorphisms in beta.2-adrenergic receptor; 4) Variation in drug response related to haplotypes of angiotensin receptor 1 (AGTR1) gene	Uses HAP and *DecoGen Informatics System* technology to measure variation in pharmaceutically relevant genes and to define genomic sub-groups with different responses to the drug. Offer services such as DNA banking, association analysis and diagnostic test development. Conducting several studies involving the pharmacogenomic profiling of licensed drugs to identify sub-populations that respond well or are at risk of ADRs. The goal of this research is the development of diagnostic tests.	*Preclinical testing and early stage trial design/ monitoring* – Pre-clinical drug metabolism studies, genotyping, sample banking and diagnostic test development. *Later stage trial design and monitoring to target 'good responders'* - Association studies of efficacy using *HAP* technology and their *DecoGen Informatics System*. Genotyping and support services. STRENGTH Trial identified genetic basis of response to statin drugs – data used in drug development by AstraZeneca.	*Preclinical testing and early stage trial design/ monitoring* – **Sells *FAMILION* to identify subjects at risk of Long QT Syndrome.** *Later stage trial design and monitoring to target 'good responders'*– **development of test for good responders to vilazodone (an SSRI) for depression (with Merck KGaA).** Co-development of new drug. *Pre-prescription screening to identify patients at risk of ADRs* – **Developing diagnostic tests to identify patients at risk of ADRs (for Clozapine). Sells *FAMILION* to identify cardiac patients at risk of Long QT Syndrome.** *Pre-prescription screening to identify 'good responders'* – **STRENGTH Trial identified genetic basis of response to statin drugs. Aims to develop diagnostic test.** **Identified genetic markers to predict response of asthma patients to albuterol -diagnostic test developed with Becton Dickinson.** *Use of efficacy data in drug marketing and in extending patent life* – Selling data on genetic basis of statin response to improve marketing of drugs.
Millennium www.millennium.com USA	1993 Public	1530 (2004) 316.8 m $ (2003)		0	Millennium conducts detailed studies of gene expression, molecular pathways and genetic differences to identify the appropriate target populations for their new drugs. They are using these techniques specifically in the development of new cancer drugs.		*Discovering new drugs which work well in entire population* – Use of broad technology platform. *Discovering new drugs aimed at genomic sub-populations* – Use of broad technology platform. *Later stage trial design and monitoring to target 'good responders'*– Use of broad technology platform. *Stratification of diseases and infectious agents into sub-types* - Use of broad technology platform.

Name and location	Age and size			Technology and business strategy			
Name Web site Country	**Started Public/ private**	**No. staff R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Myriad Genetics www.myriad.com USA	1992 (?) Public	511 (2004) 50.7 m $ (2004)		27 (mainly very general) Patents on a range of genes, including TMRSS, BRCA1 and 2 and MTS2, involved in melanoma, prostate, breast and other cancers. Claims cover diagnosis, prognosis and selection of therapy.	Myriad's research and development is focused on the discovery and development of therapeutic targets related to cancer and viral diseases. Developing diagnostic products that assess a risk of cancer due to the presence of specific mutations in known predisposition genes. Treatment advice is then offered to high-risk patients. This includes chemoprevention in patients with specific mutations		*Stratification of diseases and infectious agents into sub-types* - **Diagnostic tests to stratify cancer patients according to specific mutations in tumours. Advice on which drug is best prescribed.**
Millennium www.millennium.com USA	1993 Public	1530 (2004) 316.8 m $ (2003)	0		Millennium conducts detailed studies of gene expression, molecular pathways and genetic differences to identify the appropriate target populations for their new drugs. They are using these techniques specifically in the development of new cancer drugs.		*Discovering new drugs which work well in entire population* – Use of broad technology platform. *Discovering new drugs aimed at genomic sub-populations* – Use of broad technology platform. *Later stage trial design and monitoring to target 'good responders'*– Use of broad technology platform. *Stratification of diseases and infectious agents into sub-types* - Use of broad technology platform.
Myriad Genetics www.myriad.com USA	1992 (?) Public	511 (2004) 50.7 m $ (2004)		27 (mainly very general) Patents on a range of genes, including TMRSS, BRCA1 and 2 and MTS2, involved in melanoma, prostate, breast and other cancers. Claims cover diagnosis, prognosis and selection of therapy.	Myriad's research and development is focused on the discovery and development of therapeutic targets related to cancer and viral diseases. Developing diagnostic products that assess a risk of cancer due to the presence of specific mutations in known predisposition genes. Treatment advice is then offered to high-risk patients. This includes chemoprevention in patients with specific mutations		*Stratification of diseases and infectious agents into sub-types* - **Diagnostic tests to stratify cancer patients according to specific mutations in tumours. Advice on which drug is best prescribed.**

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
PGx diagnostics firms							
Celera Diagnostics www.celeradiagnostics.com USA	2001 Public	220 (2004) 43.8 m $ (2004)		0	Celera are conducting gene-disease association studies and host response studies to treatments for heart disease, breast cancer, Alzheimer's disease, autoimmune and inflammatory diseases including rheumatoid arthritis and diabetes. This information will be incorporated into new diagnostic tests. In the future it may be used to stratify patient populations in clinical trials to include 'good responders'. They are conducting host-response studies in Hepatitis C patients to identify those who respond positively to interferon treatment.	*Pre-prescription screening to identify 'good responders'* – Future development of diagnostic tests. *Stratification of diseases and infectious agents into sub-types* - ***ViroSeq HIV-1 Genotyping System*** **to detect mutations in the HIV virus that correlate with drug resistance.**	
DNAPrint Genomics http://www.dnaprint.com/ USA	2000 Public	12 (2003) 2.7 m $ (2003)		0	Identify genetic markers that affect a patient's variable response to certain drugs and make predictive pharmacogenomic tests. Offer a clinical genotyping service and association studies to detect patient response to certain drugs.	*Pre-prescription screening to identify patients at risk of ADRs – Pre-prescription screening to identify 'good responders'* **Dev. Ovanome diagnostic test to identify non-responders to chemotherapy (Taxol and Carboplatin). Developing Statinome diagnostic test to identify those at risk of ADRs and good responders to statins.**	
Genelex Corp. www.genelex.com **USA**	**1987** **Private**			**0**	**Produces and markets pharmacogenomic tests based on variations in the CYP genes. They are designed to determine patient candidacy and dosage of many prescribed drugs. They are marketed for the prevention of serious ADRs.**	***Pre-prescription screening to identify patients at risk of ADRs*** **- DNA Drug Reaction Profiles.**	

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Genomas http://www.genomas.net **USA**	**2003** **Private**			**0**	**Uses its PhysioGenomics technology to develop novel diagnostic products to predict an individual's response to drugs. They are designed to provide doctors with the tools to prescribe optimum drug regimens to each patient and enable the detection of patients susceptible to ADRs.**		***Pre-prescription screening to identify patients at risk of ADRs*** **- PhysioTypes using PysioGenomics Technology.** ***Pre-prescription screening to identify 'good responders'*** **- PhysioTypes using PysioGenomics Technology.**
Genomic Health www.genomichealth.com **USA**	**2000** **Private**			**0**	**Developing oncogenomic tests that will enable the stratification of cancer patients for new and existing therapies.**	***Later stage trial design and monitoring to target 'good responders'*** **– Genotyping of tumours to predict drug response. Clinical genotyping and association studies of efficacy.**	***Stratification of diseases and infectious agents into sub-types*** **- Onco*type* Breast Cancer Assay for use in clinical practice to predict the magnitude of chemotherapy benefit in breast cancer patients. Developing test to predict response to EGFR class of drugs**
Gentris www.gentris.com USA	2001 Private			0	Provides genotyping and screening services for PGx studies in clinical trials	*Pre-clinical testing and early stage trial design/ monitoring* - Genotyping and support services to ensure a representative patient population in clinical trials. *Later stage trial design and monitoring to target 'good responders'* - Clinical association studies, genotyping and support services to identify 'good responders'.	*Pre-clinical testing and early stage trial design/ monitoring* - **Panels of ADME gene variant assays (including CYP).** *Pre-prescription screening to identify patients at risk of ADRs* **- Pharmacogenomic tests based on CYP2D6 and CYP2C19 are in development.** *Pre-prescription screening to identify 'good responders'* – Tests in development for a number of common conditions.
Interleukin Genetics www.ilgenetics.com USA	1986 (ReInc. 2000) Public	28 (2004) 2.0 m $ (2003)		13 Number of patents covering diagnostic tests for predisposition and therapeutics for a range of diseases involving cytokine genes, including; obstructive airway disease, early-onset menopause, restenosis, osteoporosis, sepsis, cardiovascular disorders, coronary artery disease, asthma.	Studies the genetics of inflammation and researching how variations in IL-1a, IL-1b and IL1RN genes affect individual response to drug therapy. Conducting clinical trials that analyse the response to Enbrel, Remicade or Kineret therapy in rheumatoid arthritis patients with the aim of developing a pharmacogenetic test that will personalise therapy in RA by matching patients to their most effective treatment.		*Pre-prescription screening to identify 'good responders'* – Aim to develop a diagnostic tests to match patients to their most effective therapy for RA. **Have produced pharmacogenetic test to predict response to asthma drugs.**

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Prediction Sciences http://www.predict.net USA		Private		0	GeneRx technology can predict diagnostic markers that determine individual response to therapy. Offer patient sampling, genotyping, comprehensive analysis and the co-development of personalised medicine diagnostics.	*Pre-clinical testing and early stage trial design/ monitoring* - Genotyping, studies of metabolism and toxicity. *Later stage trial design and monitoring to target 'good responders'* - GeneRx to identify good responders.	*Pre-prescription screening to identify patients at risk of ADRs* - **GeneRx Diagnostics for hypertension drugs. Neurological GeneRx to predict response in patients with schizophrenia, bipolar disorder and depression** *Pre-prescription screening to identify 'good responders'* – **GeneRx Diagnostics for hypertension drugs. Neurological GeneRx to predict response in patients with schizophrenia, bipolar disorder and depression.** **Oncology GeneRx diagnostics.**
Prometheus Laboratories http://www.prometheus-labs.com USA		Private		-	Provides pharmacogenetic evaluations to assist in therapy management. Licensed their PRO-PredictRx TPMT diagnostic test to Genaissance.		*Pre-prescription screening to identify patients at risk of ADRs* – **PRO-PredictRx TPMP genotypic test to determine patient candidacy for AZA/6-MP therapy and to individualise dosage in rheumatoid arthritis.**
Third Wave www.twt.com USA	1993 Public	156 (2003) 12.0 m $ (2003)		0	Invader technology can be used by researchers and clinics to identify genetic variation that influences drug response, and in the stratification of infectious diseases.	*Stratification of diseases and infectious agents into sub-types* - Genotyping and stratification of infectious diseases using Invader technology.	*Pre-prescription screening to identify patients at risk of ADRs* - **SNP genotyping and CYP2D6 gene variation kits.** Other CYP variants in development. *Stratification of diseases and infectious agents into sub-types* - **HCVGASRs all six of the major Hepatitis C genotypes**.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
ViroLogic www.virologic.com USA	1995 Public	250 (2005) 7.8 m $ (2004)		?	Developed drug resistance assays for the genotyping and management of HIV. Developing similar assays for hepatitis B and C and cancer. Offer pharmacogenomic testing services during drug development.		*Discovering new drugs aimed at genomic sub-populations and discovering new drugs that work well in entire population* - use of PhenoSense and GeneSeq HIV tests. Developing similar tests for HCV and cancer (EGFR/ Her receptor family). *Later-stage trial design and monitoring to target 'good responders* - use of PhenoSense HIV and GeneSeq tests. Developing similar tests for HCV and cancer (EGFR/Her receptor family). *Stratification of diseases and infectious agents into sub-types* – **use of PhenoSense and GeneSeq HIV tests. Developing similar tests for HCV/ HBV and cancer (EGFR/Her receptor family).**
PGx Service Firms							
First Genetic Trust www.firstgenetic.net USA	Private			0	Provides an information technology platform and services to support collaborative genetic and pharmacogenetic research. This consists of two web-based applications, enTRUST Study Management and enTRUST Genetic Bank.		

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. alliance.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Gene Logic www.genelogic.com USA	1994 Public	400 (2003) 2.1 m $ (2003)		?	Developed two genomic-based databases that can be used by researchers to determine the potential toxicity of drug candidates. These databases have the potential to stratify patient populations in clinical trials to identify those who may be the most responsive to particular drugs.	*Discovering new drugs which work well in entire population* - BioExpress and ToxExpress Systems. *Discovering new drugs aimed at genomic sub-populations* - BioExpress and ToxExpress Systems. *Preclinical testing and early stage trial design/ monitoring* – ToxExpress System *'Rescue' of products in late stage trials (ADRs)* – drug repositioning and selection technologies *Later-stage trial design and monitoring to target 'good responders* - BioExpress System *Drug rescue (efficacy)* - drug repositioning and selection technologies	
Genizon BioSciences (Galileo Genomics) http://www.galileogenomics.com Canada	Private	85+ (2004)		0	Chromozoom technology and the Quebec linkage Disequilibrium Map to discover biomarkers associated with drug efficacy and ADRs. Provide pharmacogenomic services to enhance safety and efficacy in drug development.	*Discovering new drugs aimed at genomic sub-populations* - association studies of drug response. *Preclinical testing and early stage trial design/ monitoring* – discovery of genes and biomarkers associated with ADRs. *Later-stage trial design and monitoring to target 'good responders* – discovery of genes and biomarkers associated with efficacy. Chromozoom technology and genotyping to stratify patient population.	

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Genomics Collaborative www.genomicsinc.com USA	Private			0	Provides resources for pharmacogenomic marker discovery. Their technology platform offers customised access to GCI's Global Repository of clinical samples. They also offer support services for clinical genotyping.	*Discovering new drugs aimed at genomic sub-populations* - GCI Access to validate genomics-based drug and diagnostic targets. *Pre-clinical testing and early stage trial design/ monitoring* - Genotyping, DNA and tissue banking.	
Perlegen Sciences http://www.perlegen.com USA	2000 Private			0	Carry out whole genome association studies to predict the safety and efficacy of prescription drugs. They are also discovering the genetic variants associated with disease for the development of new diagnostics and therapeutics. **Identifying SNPs that are predictive of efficacy or adverse events and incorporate them into diagnostic tests.** They offer to 'rescue' drugs whose clinical development would have been otherwise discontinued.	*'Rescue of products in late stage trials (ADRs)* - Retrial in population selected by genotype. *Later stage trial design to identify 'good responders'*- Clinical association studies. *Drug Rescue (efficacy)* - Retrial in population selected by genotype. *Market (label) extension of products restricted by ADRs* - Association studies of safety. *Post-marketing surveillance* – Association studies of safety *Pre-prescription screening to identify 'good responders'* and *use of efficacy data in drug marketing* — Association studies of efficacy. *Stratification of diseases and infectious agents into sub-types* – Association studies	*Discovering new drugs aimed at genomic sub-populations* – Internal drug discovery programme
Seryx www.signaturegenetics.com USA	Private			0	Provide an information service called Signature Genetics to doctors with up-to-date information based on the latest scientific advances. Customised information for individual patients can be requested based on molecular genetic testing and answers to a questionnaire. The report provided gives details of what medications the patient is likely to respond well or suffer adverse reactions to and at what dose.	*Pre-prescription screening to identify patients at risk of ADRs* - Signature Genetics. *Pre-prescription screening to identify 'good responders'* – Signature Genetics.	.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Viral Therapeutics Inc. http://www.viraltherapeutics.com USA	1995 Private			0	Pharmacogenomics services for drug discovery enable responder/ non-responder disease association studies, the identification of therapeutic benefit and toxicity profiles and the validation of new targets for therapy.	*Preclinical testing and early stage trial design/ monitoring* – Clinical association studies. *Later stage trial design to identify 'good responders'*- Genotyping, drug metabolism and toxicity studies.	*Preclinical testing and early stage trial design/ monitoring* – Diagnostics for clinical genotyping. *Later stage trial design to identify 'good responders'*- Diagnostics for clinical genotyping.
PGx Tools, Kits and Software Firms							
Affymetrix www.affymetrix.com USA	1992 (Re-Inc 1998) Public	871 (2003) 65.9 m $ (2004)		0	Developed GeneChip technology to for use in drug discovery and development. GeneChips enables researchers to study DNA variation across the whole genome or in areas of interest. They can be used to predict patient response to therapy in a number of disease areas. Custom Sequencing Arrays can be used to understand heterogeneity between patients and its impact on drug response.		*Pre-clinical testing and early stage trial design/ monitoring* - Application of GeneChip technology for genotype-based toxicity studies. *Drug rescue (efficacy)* - GeneChip Human Genome U133 Plus 2.0 Arrays can be used to correlate gene expression levels with adverse events. *Later stage trial design and monitoring to target 'good responders'* - GeneChip Human Genome U133 Plus 2.0 Arrays can be used to correlate gene expression levels with good response. Collaboration with deCODE genetics, and Stanford School of Medicine using global gene expression patterns from prostate cancer to distinguish location of tumours, stage of disease, and responsiveness of potential drug therapies
Golden Helix Inc. www.goldenhelix.com USA	1998 Private			0	Provides HelixTree software for pharmacogenetics research. The software analyses clinical trial data and can predict drug efficacy and side effects.		*Pre-clinical testing and early stage trial design/ monitoring* - HelixTree. *Later stage trial design and monitoring to target 'good responders'* – HelixTree

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Nanogen www.nanogen.com USA	Public	137 (2003) 19.0 m $ (2003)		0	NanoChip Technology can screen for various DNA sequences and differentiate between SNPs. The system may help to stratify patients during clinical trials and identify those receiving maximum benefit from the treatment.		*Pre-clinical testing and early stage trial design/ monitoring* - NanoChip. *Later stage trial design and monitoring to target 'good responders'* – NanoChip
Sequenom www.sequenom.com USA	1994 Public	207 (2003) 25.4 m $ (2003)		0	Provide pharmaceutical companies with the tools to include pharmacogenetic data in their clinical trials. MassARRAY technology platform can be used to perform locus-specific or genome wide scans across populations of patients assessed for pharmacological responses to drugs. This data can be used to tailor clinical trials, save failed drugs and develop drugs for sub-populations. Developing cell-based assays for a wide variety of targets. These can be used to test the efficacy or potential toxicities of potential new and existing drug candidates.	*Discovering new drugs aimed at genomic sub-populations* - Potential application for MassARRAY technology *Pre-clinical testing and early stage trial design/ monitoring* - Application of MassARRAY technology. *Later stage trial design and monitoring to target 'good responders'* - Application of MassARRAY technology.	
Tm Biosciences www.tmbioscience.com Canada	Public	3.02 m $ (2003)		0	Developing and commercialising diagnostic tests based on the Tm100 Universal Array. Pharmacogenomic Tag-IT Mutation Detection Kits are centred on the P450 enzyme system.		*Pre-clinical testing and early stage trial design/ monitoring* – **Use of CYP genotyping chip to detect variations in drug metabolism.** *Pre-prescription screening to identify patients at risk of ADRs* - Use of CYP genotyping chip to detect variations in drug metabolism.

Name and location	Age and size			Technology and business strategy			
Name **Web site** **Country**	**Started** **Public/ private**	**No. staff** **R&D spend p.a.**	**No. allianc.**	**No. Patents**	**Involvement in PGx**	**PGx-related services (technical option)**	**PGx-related products (technical option)**
Waban Software www.wabansoftware.com USA	2002			0	Waban Explorer-PGx is a commercially available pharmacogenetics data management software tool. It allows the analysis of data from multiple therapeutic areas and provides a variety of analytical tools. Configurable reports present users with detailed genetic information such as assay, genotype and gene sequence information and adverse event data.		*Pre-clinical testing and early stage trial design/ monitoring* - Waban Explorer-PGx informatics tool. *Later stage trial design and monitoring to target 'good responders'* – Waban Explorer PGx informatics tool

Annex 3: Firms with a minor interest in PGx

Name	Country	Founded	Focus	Involvement in PGx
North American Firms				
Amgen www.amgen.com	USA	1980	Drug discovery	Have carried out pharmacogenetic studies on PEG sTNF-RI for the treatment of Rheumatoid Arthritis. The object of this research is to find critical genes involved in RA and other autoimmune inflammatory diseases, which could lead to the development of new therapies that target those genes.
ARCA Discovery No website	USA		Drug development	Have licensed the beta-blocker Bucindolol from Incara Pharmaceuticals and Indevus Pharmaceuticals. The development of Bucindolol for the treatment of heart disease was discontinued in 1999. During pharmacogenetic studies, ARCA have identified sub-populations that are ideally suited for Bucindolol treatment.
Cardinal Health www.cardinal.com	USA	1994	Drug development	Provide pharmacogenomic services in drug discovery programmes. Screening of patient population though P450 isozyme analysis.
Ellipsis www.ellipsisbio.com	Can	1997	Drug development	Offers a SNP genotyping service for academic, industry and government clients and custom assay development, SNP validation and data analysis. They are in the early stages of identifying genes associated with Alzheimer's disease and IBD with future plans to develop pharmacogenetic tests and customised therapeutics.
GeneOhm Sciences www.geneohm.com	USA	2001	Diagnostics	Develops and supplies molecular diagnostic products for the drug discovery and clinical trial markets. Their technology platform can identify SNPs linked to disease and has applications in personalised medicine. In 2003 they licensed MTHFR gene patent rights from Variagenics with the view to developing diagnostic tests for personalised medicine.
InSite Vision www. insitevision.com	USA	1987	Diagnostics	Have developed the OcuGene glaucoma genetic test. From the results of this test patients who are at risk of a more severe form of the disease can be identified. This enables the tailoring of treatment regimens.
NeoPharm www.neophrm.com	USA	1995	Drug development	Conducting clinical trials involving the genotyping of cancer patients to establish safe-dose levels of their NeoLipid compound LE-SN38. This is based upon the UGT1A1 genotype, which is an enzyme made in the liver that metabolises LE-SN38.
Panacea Pharmaceuticals www.panaceapharma.com	USA	1999	Diagnostics	Researching the HAAH cell surface antigen as a target for cancer drugs and diagnostics. Proteus Diagnostics, a wholly owned subsidiary is focused on developing and commercialising pharmacogenomic and pharmacoproteomic tools for cancer detection, diagnosis and treatment selection. They are currently developing cancer diagnostics based on the over-expression of HAAH in tumours.
PolyGenyx www.polygenyx.com	USA	1998	Diagnostics	Applying HaploScan technology to the development of diagnostic tests based on the analysis of disease-related haplotypes and genotypes, for conditions such as cancer, diabetes, and cardiovascular disease. Also focused on the development of HaploScan assays related to drug metabolising enzymes for pharmacogenetic applications. Pharmacogenetic diagnostics are in development.

Name	Country	Founded	Focus	Involvement in PGx
TriPath Imaging www.tripathimaging.com	USA		Diagnostics	TriPath imaging is using its image analysis technology to analyse the pharmacological effect of a cancer therapeutic with Bristol-Myers Squibb. The data generated will be used to evaluate patient response across varied dosing levels based on changes in tumour marker levels before and after treatment. TriPath Oncology have developed reagents for pharmacogenomic testing in cancer.
European Firms				
AdnaGen www.adnagen.com	Ger	1998	Diagnostics	They have developed pharmacogenetic test kits with Artus to detect polymorphisms in drug metabolising enzymes (CYP) and can be used during drug development to reduce the risk of ADRs in the patient population.
ExonHit www.exonhit.com	Fra	1997	Drug discovery & development	Historic interest in PGx. Currently investigating deregulation of RNA splicing through polymorphisms in the CYP genes and the effect this has on drug metabolism. Applications in drug discovery and development.
GeneScan Europe www.genescan.com	Ger		Drug development	Use of Pharm-O-Kin biochip platform for CYP2D6*4 genotyping
HepCgen www.hepcgen.com	UK		Diagnostics	Have developed Hepatitis C genetic tests to tailor treatment to individual patients and to identify patients unlikely to respond to treatment. These tests are available in the UK.
IntegraGen www.integragen.com	Fra	2001	Diagnostics	In early stages of PGx research using gene mapping technology to identify genes associated with multi-factorial disease such as obesity and diabetes. Their future outlook is to develop therapeutics and pharmacogenomic diagnostics targeted towards these genes.
Memorec Biotec www.memorec.com	Ger	1997	Diagnostics	PIQOR is a gene expression platform that has pharmacogenomic applications during drug discovery and development. It is also developing diagnostics to support tailor-made therapies for patient treatments.
PharmaMar www.pharmamar.com	Spain	1986	Drug development	Undertaking pharmacogenetics research on three pre-clinical anticancer drugs Yondelis, Aplidin and Kahalalide F with the aims of providing a customised chemotherapy model for individual patients.
Solvo Biotechnology www.solvobiotech.com	Hungary	1999	Drug development	Provides pharmaceutical companies with predictive ADME assays for use during drug development. Have developed the MultiDrugQuant diagnostic kit to determine the level of multidrug resistance of tumour cells. This phenotypic test can help physicians determine disease prognosis and plan personalised treatment regimens.

Annex 4: Industrial interest in the main technological options for PGx

Drug discovery	No. of companies interested in the field	Internal	Services	Product
1. Discovering new drugs which work well in entire population	**8**	Millennium	**Gene Logic, Astex, Brain Resource, CXR (CYP), DxS (ADME)**	ViroLogic, Epidauros, CXR (CYP)
2. Discovering new drugs aimed at genomic sub-populations	**9**	Millennium, Perlegen	**Curagen, Gene Logic, Genizon, Genomics Collaborative, Sequenom, Brain Resource**	ViroLogic
Safety of drugs in development				
3. Pre-clinical testing and early stage trial design/ monitoring	**24**		**Curagen, Genaissance, Gentris (ADME), Prediction Sciences, Gene Logic, Genizon, Genomics Collaborative, Viral Therapeutics, Sequenom, Epidauros, Brain Resource, CXR, DxS, Medigenomix**	Genaissance (1), Gentris (CYP), Viral Therapeutics, Affymetrix (Chip), Golden Helix (sw), Nanogen (Chip) Tm Biosciences (CYP), Waban, Epidauros, Jurilab (ADME chip), LGC (ADME), TheraStrat, CXR (CYP), Amersham (CYP chip), Biotage (CYP chip)
4. 'Rescue' of products in late stage trials (ADRs)	6		Gene Logic, Perlegen, Astex, Epidauros, CXR	Epidauros, TheraStrat
Efficacy of drugs in development				
5. Later stage trial design and monitoring to target 'good responders'	**23**	Millennium	**Egeen, Genaissance, Genomic Health, Gentris, Prediction Sciences, Gene Logic, Genizon, Perlegen, Viral Therapeutics, Sequenom, deCODE, Epidauros, Ipsogen, Brain Resource, DxS, Medigenomix**	Genaissance (2), ViroLogic, Viral Therapeutics, Affymetrix (Chip), Golden Helix (sw), Nanogen (Chip), Waban (sw), Axis-Shield, Vita Genomics
6. Drug rescue (efficacy)	4		Gene Logic, Perlegen, Epidauros	Affymetrix (Chip), Epidauros
Safety of licensed drugs				
7. Market (label) extension of products restricted by ADRs	1		Perlegen	
8. Pre-prescription screening to identify patients at risk of ADRs	**11**		Genelex (CYP), Perlegen, Seryx	**Genaissance (3), DNAPrint, Genomas, Gentris (CYP), Prediction Sciences, Prometheus (TPMT), Third Wave (CYP), Tm Biosciences (CYP)**
9. Post-marketing surveillance	2		Perlegen	TheraStrat

Drug discovery	No. of companies interested in the field	Internal	Services	Product
Efficacy of licensed drugs				
10. Pre-prescription screening to identify 'good responders'	**16**		Seryx	**Egeen, Genaissance (4) (5), Celera, DNAPrint, Genomas, Gentris, Interleukin, Prediction Sciences, deCODE, Axis-Shield, Epigenomics, Jurilab, LGC, Vita Genomics, DxS**
11. Use of efficacy data in drug marketing and in extending patent life	3			Egeen (patent), Genaissance (6), Axis-Shield (patent)
Stratification of diseases and infectious agents into sub-types				
12. Stratification of diseases and infectious agents into sub-types	**10**	Millennium	Perlegen, Epigenomics, Vita Genomics	**Myriad, Celera, Genomic Health, Third Wave (HCV), ViroLogic (HIV) Dakocytomation, Epigenomics, Ipsogen (Chips), Vita Genomics**

Source: SPRU patent analysis 2005

Annex 5: Commercial PGx tests currently in use

Test name	Focus/ disease	Company	Applications
Drug metabolism			
CYP2D6/ 2C9/ 2C19/ 1A2	Drug metabolism	Genelex	Laboratory screening service for variation in CYP genes to help physicians predict individual responses to many prescription, OTC and herbal medicines (including warfarin, Prozac, Zoloft, Paxil, Tamoxifen, and Valium) in order to prevent ADRs.
Tag-It CYP2D6/ 2C9/ 2C19 Mutation Detection Kits	Drug metabolism	Tm Biosciences	P450 genetic test kits to identify patients with atypical drug metabolism at risk of ADRs. Sold to companies who wish to include pharmacogenetic data with their new drug submissions.
CYP2D6 ASR kit	Drug metabolism	Third Wave Molecular Diagnostics	Kit for laboratory genetic testing of major variant in a key drug metabolising gene. Allows patients to be classified according to their rate of drug metabolism and aims to be a pre-prescription aid to establish dosing levels in order to prevent ADR's.
DME variant genotyping	Drug metabolism	Gentris	Research and clinical genotyping services using CYP, NAT2 and other drug metabolising enzymes for pre-clinical and clinical drug development studies.
P450 isoenzyme analysis	Drug metabolism	Cardinal Health	Research services to support drug development
CYP450 Pyrosequencing assay	Drug metabolism	Biotage	Genotyping and SNP analysis for companies planning to include pharmacogenetic data with their new drug submissions.
CYP3A/2D6 & MDR1 profiling assay	Drug metabolism	Epidauros Biotechnologie	Genetic test to include patients that are more likely to have a beneficial therapeutic response and less likely to suffer ADRs in clinical trials.
Pharmacogenetic test kits	Drug metabolism	AdnaGen	Genotyping kits to detect polymorphisms in drug metabolising enzymes; can be used during the drug development process to reduce the risk of ADRs in the patient population. Developed by AdnaGen and sold through Artus.
DrugMEt Genotyping Test	Drug metabolism	Jurilab	Drug metabolising enzyme microarray test to identify the presence of 27 SNPs in drug metabolising genes and the deletion/duplication of the CYP2D6 gene. Main use is the identification of genetically mediated metabolic patterns in clinical trials.
HyBeacon Assays	Drug metabolism	LGC	Assays developed to detect and distinguish variation in medically relevant genes for use by doctors or pharmacists to adjust medications to suit the individual's ability to derive therapeutic value from certain prescribed drugs.
CodeLink p450 SNP Bioarray	Drug metabolism	Amersham Biosciences	Designed for broad based toxicogenomic screening of clinical trial populations and the discovery of novel associations between P450 genotype and phenotype.
Pharm-O-Kin biochip	Drug metabolism	GeneScan Europe	High throughput pharmacogenetic typing for use in drug development to optimise the design of clinical trials.

Test name	Focus/ disease	Company	Applications
PRO-PredictRx TMPT Genetics	Drug metabolism/ Rheumatic disease	Prometheus Laboratories	Test measures the level of TMPT enzyme activity in patients with rheumatic disease to determine candidacy and dosage for IMURAN (Azathioprine) and 6-mercaptopurine) therapy.
Anti-viral drug resistance			
ViroSeq	**HIV viral genotyping**	Celera Diagnostics	HIV-1 genotyping to detect drug resistant strains and mutations. Allows patient stratification for appropriate treatment regimen selection.
Hepatitis C Virus (HCV) genotyping kit	HCV viral genotyping	Third Wave Molecular Diagnostics	Reagents for laboratory genetic testing to classify the hepatitis virus into one of six major subtypes. Allows improved treatment, as viral subtypes have different drug resistance profiles
GeneSeq HIV test	HIV viral genotyping	ViroLogic	**Genotypic drug resistance assay used to devise effective personalised treatment strategies for people living with HIV.**
HCV Genotyping	Hepatitis C	HepCgen	Test for viral genotyping to allow anti-viral treatments to be tailored to individual patients and the identification of patients unlikely to respond. It is commercially available in the UK.
Cancer (disease stratification)			
Onco*type* DX	Breast cancer	Genomics Health	Diagnostic assay based on a panel of 21 genes to identify sub-types of breast cancer. Used to enhance treatment by quantifying the likelihood of breast cancer recurrence in women with newly diagnosed stage 1 or 2 breast cancer treated with tamoxifen.
BRACAnalysis	Breast cancer	Myriad Genetics	Test assesses a woman's risk of developing breast or ovarian cancer based on the presence of common mutations in the BRAC1/2 genes. Chemoprevention advice is then offered e. g. Tamoxifen for women with BRAC1/2 mutations.
HER2 FISH PharmDx	Breast Cancer	Dakocytomation	Diagnostic test based on the detection of a specific protein caused by the over-expression of the HER2 gene. It is used for the selection of breast cancer patients for Herceptin therapy.
EGFR PharmDx	Colorectal Cancer	Dakocytomation	Diagnostic assay is approved for use to identify patients with colorectal cancer who will respond to treatment with ERBITUX.
FusionQuant and MLL FusionChip	Leukaemias	Ipsogen	Standardised assay and molecular diagnostic chip to detect the presence and guide the treatment of certain cancers (ABL and MLL).
Other conditions			
Familion test	Risk of Long-QT syndrome	Genaissance	Genetic test for cardiac channelpathies (familial Long QT syndrome and Brugada Syndrome – that cause sudden cardiac death. These can be caused as a result of rare ADRs.
Response to asthma therapy	Asthma	Genaissance	Genetic test to determine response to albuterol therapy (beta2-adreneric receptor gene) developed with Becton Dickinson.
OcuGene glaucoma genetic test	Glaucoma	InSite Vision	Genetic test to identify patients at risk of more aggressive form of glaucoma and to guide therapy.
Diastat	Rheumatoid Arthritis	Axis-Shield	Test to stratify RA patients for treatment with disease modifying anti-rheumatoid drugs (DMARDs)

Annex 6: Commercial PGx tests currently In development

Test name	Focus/ disease	Company	Applications	Stage of development
Drug metabolism				
CYP2D6 and CYP2C19 Genotyping kits	Metabolism of many common drugs	Gentris	Developing their kits as pre-prescription diagnostic tools for providing point-of-care genetic testing to physicians.	Initial release as "investigational use only"/ Seeking FDA approval.
Anti-viral drug resistance				
GeneSeq HBV	Hepatitis B	ViroLogic	Genotypic hepatitis B test to guide the treatment of disease by optimising treatment regimens.	Phase III (Patient testing)
GeneSeq HCV	Hepatitis C	ViroLogic	Genotypic hepatitis C test to guide the treatment of disease by optimising treatment regimens.	Phase III (Patient testing)
Hepatitis B and C Genotyping Test	Hepatitis B and C	Vita Genomics	DNA-based diagnostic tests to enable patient stratification into groups suitable for mono and combinational therapies using existing interferon alpha drugs according to viral genotype.	Seeking pharmaceutical/ biotech companies for commercialisation.
Cancer (disease stratification)				
Ovanome	Ovarian Cancer	DNAPrint Genomics	SNP-based diagnostic tool predictive of non-response to the Taxol and Carboplatin drug chemotherapy combination in ovarian cancer.	Awaiting clinical testing / clarification of FDA guidelines on pharmacogenomics.
LE-SN38 Genotyping		NeoPharm	Using genotyping of patients in pre-clinical and clinical development of their anticancer drug LE-SN38. Genotyping splits responders into regular and slow metabolisers, and allows dose safety adjustments.	LE-SN38 in phase 1/2 clinical trials
EGFR/Her receptor family	Various cancers	ViroLogic	Developing test to enable physicians to identify the appropriate course of treatment for cancers that have a particular molecular profile.	Early clinical studies
Predictive test for response to anti-cancer drugs	Cancer	DxS	Developing test to detect the presence of EGFR gene mutations in tumours that can be used to identify good candidates for Iressa and other EGFR targeted drugs.	Uncertain
Pharmaco-diagnostic test	Breast Cancer	Epigenomics	Developing test to predict the probability of relapse following treatment with Tamoxifen in breast cancer patients.	Pre-clinical (marker validation). Clinical development will be carried out by Roche.
ProfileChip	Breast cancer	Ipsogen	Gene expression-based chip to characterise sub-types of breast cancer and assist in the management of therapy.	Validation of gene expression signature. Awaiting clinical studies.

Test name	Focus/ disease	Company	Applications	Stage of development
Other conditions				
Statinome	Various cardiac disease, high cholesterol	DNAPrint Genomics	Developing tests to predict response to statins.	Planned to enter clinical trials in early 2005
Vilazodone & test	Depression (SSRI)	Genaissance	Vilazodone is a small molecule compound licensed from Merck AG, for the treatment of depression. Planning to start clinical studies in order to find genetic markers that can identify a population of patients who will respond to the drug.	Entering Phase 2 clinical trials in 2005, at which stage begins the test development.
Statin test	Hypercholes-terolaemia	Genaissance	Conducted STRENGTH Trail to find correlation between genetic variation and response to statin treatment for high cholesterol. In process of developing a predictive response test from this data.	Uncertain
Clozapine test	Schizophrenia	Genaissance	Identifying genetic variations associated with risk of developing agranulocytosis when treated with clozapine.	Initial study still in progress
Rheumatoid Arthritis diagnostic	Rheumatoid Arthritis (RA)	Interleukin Genetics	Conducting clinical trials that analyse the response to Enbrel, Remicade or Kineret therapy in RA patients who have inherited common variations in the IL-1 and TNFa genes. Aim is to produce a test that will personalise RA therapy.	Initial clinical discovery stage entered
Asthma drugs	Asthma	Interleukin Genetics	Identified markers and developing test to predict an individual's response to different asthma drugs.	Uncertain
Hypertension R_x	Hypertension	Prediction Sciences	Developing test to predict which anti-hypertensive therapy (ACE, Ca-Channel or ARB Inhibitor, diuretic, ß-Blocker, combination) would be most effective for lowering blood pressure.	Late clinical studies
Neurological R_x	Depression (Paxil) and schizophrenia (Clozapine)	Prediction Sciences	Developing tests to predict response to treatments for depression, bipolar disorder and schizophrenia.	Early clinical studies
Asthma drugs	Asthma	deCODE	Identified genetic markers predicting response to asthma drugs. Developing pharmacogenetic test with Roche Diagnostics.	Unknown
Anti-hypertension drugs	Hypertension	deCODE	Identified genetic markers predicting response to anti-hypertension drugs. Developing pharmacogenetic test with Roche Diagnostics.	Unknown
HeartGEn	Myocardial infarction and ischaemic stroke	Jurilab	Genetic test to provide additional information to help identify patients most at risk of MI or stoke, and to assist in choice of preventive treatment.	Prototype being tested

Annex 7: Large company collaborations in PGx

Company (Buyers)	Partner (Sellers)	Date	Deal size	Recap categories / description
Abbott	Genset	1997	42.5 m $	Genedrug response associations. Diagnostics (already licensed)
	Visible Genetics	2000		Provision of HIV genotyping in two clinical studies of protease inhibitor
	Celera Diagnostics	2002		Collaboration, co-development, research. *In vitro* diagnostic products.
Amersham Pharmacia Biotech	Avitech Diagnostics	1997		Rights to EMD mutation scanning technology (research and diagnostics)
	DNA Sciences	2001		Collaboration to develop DNA analysis and SNP profile technology
(DNA Sciences)	Amersham Pharmacia Biotech	2000		Purchase of genotyping systems
(GE Healthcare)	Amersham	2003	9.5 b $	Acquisition. Acquisition of remaining shares.
Amgen	Variagenics	2001		Collaboration,development. Variagenic Impact Program (VIP) – find SNP markers of drug response
AstraZeneca	Astex Technology	2001		Structural biology to determine 3D shape of CYP variants
	Genaissance	2001		Use of PGx in target discovery
	Orchid	2001		Genotyping collaboration, inc. development of assays
	Astex Technology	2003		Extension of agreement on structure of Cytochrome P450 and drug interactions
	Dakocytomation	2003		Collaboration, license, research. Identify factors influencing clinical response to IRESSA.
	Genaissance	2003		Research, license. *DecoGen* Informatics System to investigate variable response to statin drugs.
	Epigenomics	2004		Collaboration. Tumour samples for biomarker discovery.
	Perlegen Sciences	2004		Collaboration, license, research. Myocardial infarction collaboration.
(Orchid)	AstraZeneca (Cellmark)	2001		Acquisition of genetic diversity testing business
Aventis	Incyte	2000		Discover SNP markers involved in drug metabolism
	Astex Technology	2002		Research. Cytochrome P450s crystal structure for drug discovery.
	Gene Logic	2003		License. ToxExpress and ASCENTA Systems.
	Astex Technology	2004		Extension of structural biology agreement in the area of Cytochrome P450s
RPR Gencell	Oncormed (now Gene Logic)	1997		P53 gene therapy – variant/ response association study (gene therapy)
	Gene Logic	1998		Expansion of PGx collaboration re disease genotyping
Bayer	Curagen	2001	125 m $	Pharmocogenomic and toxicogenomic services for drug discovery
	Epidauros	2001		Assays to test for stimulation of CYP enzymes (preclinical leads)
	Phase1 Molecular Toxicology	2001		Collaboration, supply. Toxicogenomic products and services
	Visible Genetics	2002	61.4 m $	Acquisition. Acquisition for cash
	Genaissance	2003		Collaboration, license. Develop pharmacogenetic markers of drug safety and efficacy.
	Amersham	2004		Development. HIV TRUEGENE assays for personalised medicine.
	The Brain Resource **Company**			Pharmacogenetic services in clinical trials.

Company (Buyers)	Partner (Sellers)	Date	Deal size	Recap categories / description
Biogen	Genaissance	2001		License. Access to HAP database for SNP's
	Genaissance	2002		PGx Collaboration for research, development and marketing
	Epigenomics	2004		Collaboration, research, equity. Biomarkers to predict responsiveness to drugs in oncology program.
	The Brain Resource **Company**			Pharmacogenetic services in clinical trials.
bioMerieux–Pierre Fabre	ExonHit	2001		Collaboration, license, research. Proofhit for cancer diagnostics
Boehringer Ingelheim	Phase1 Molecular Toxicology	2000		Toxicology screening to identify patients at risk of ADRs – established drugs
	Variagenics	2000		PGx study of drug development – find SNP markers of response. Diagnostics.
Bristol-Myers Squibb	Millennium Predictive Medicine)	1999	32 m $	PGx of cancer treatments (in development and on market) – associations data
	Orchid	2000		Sale of SNPstream genotyping system
	PPGx	2000		Purchase of PGx clinical trials management software for drug development
	DNA Sciences	2001		Association study of target gene
	Celera Diagnostics	2002		Collaboration, development, license, research. Dx and Rx for cardiovascular disease and diabetes.
	Perlegen Sciences	2002	2.2 m $	License, research. Identify markers of patient response to BMS drugs.
	TriPath Imaging	2003		License, supply. Image analysis for oncology clinical trials.
	The Brain Resource Company			Pharmacogenetic services in clinical trials.
Daiichi	**Third Wave**	2002		PGx for established chemotherapeutic – association studies and diagnostics
Ferring Pharmaceuticals	**Genaissance**	2003		**Pharmacogenetic services and technology.**
Fujisawa	**Astex Technology**	2003		**Collaboration, license, research.** Cytochrome P450 Structure for drug discovery.
GlaxoSmithKline	Curagen	1998	48 m $	Pharmacogenomics drug discovery, both safety and efficacy
	Visible Genetics	2000		Contract genotyping of HIV variants
	First Genetic Trust	2001		Study of ADRs services to support research on genedrug response association
	Golden Helix	2001		Software for PGx
	Golden Helix	*2001*		*Development. Additional functionality to HelixTree.*
	Orchid	2001		Genomewide SNP scanning – genotyping and assays
	Sequenom	2002		Genomewide SNP assay for PGx and functional genomics
	Perlegen Sciences	2002		Collaboration, license, research. Identify SNP's as markers of drug response.
	ViroLogic	2002		Collaboration, license. HIV drug development.
	ACLARA Biosciences	2004		Evaluation of eTag assays for patient selection in targeted cancer therapies
	First Genetic Trust	2004		Collaboration, research. Genetic basis for Adverse Drug Reactions.
	Perlegen Sciences	2004		Collaboration, license, research. High-density whole genome scanning.
GlaxoWellcome	Affymetrix	1997		Database of HIV genotype drug response associations

Company (Buyers)	Partner (Sellers)	Date	Deal size	Recap categories / description
SmithKline Beecham	Incyte	1997	25 m $	Formation of DiaDexus
	Orchid	2000		Sale of SNPstream genotyping system
	Third Wave	2000		SNP assays for development and use of therapeutic vaccines
(Ipsogen)	Genzyme Corp.	2004		Sub-license. WT1 gene as a biomarker in acute leukaemia.
Janssen	Genaissance	2000		PGx collaboration for research, development and marketing
Lilly	Orchid	2000		SNP scoring service
	Perlegen Sciences	2002	2.2 m $	Equity, license, research. Identify genetic markers.
	The Brain Resource Company			Pharmacogenetic services in clinical trials.
Merck	Oncormed (now Gene Logic)	1998		Analysis of mutations for clinical trials (drugs in development)
	Celera Diagnostics	2003		Collaboration, research. Cancer diagnostics.
	DeCODE	2004	10.0 m $	Collaboration, development, equity, license, warrant. Information-rich clinical trials drug development alliance.
	Genaissance	2004		Equity, license. Vilazodone (SSRI and a 5HT1A partial agaonist).
Millennium (predictive medicine)	Orchid	2000		SNP scoring service
Millennium	Genaissance	2003		License. Hap (SNP's) technology
	Gene Logic	2004	4.5 m $	License. ToxExpress System.
Mitsubishi Pharma	Astex Technology	2002		License, research. X-ray crystallography of cytochrome P450 and other Mitsubishi compounds.
Novartis	Third Wave	2000		Development of high density SNP assay
	Variagenics	2002		Identification of markers for efficacy of licensed and new cancer drugs
Novo Nordisk	Genaissance	2003		License. *HAP* technology for drug development.
Ono pharmaceuticals	Curagen	2000		Pharmacogenomics and toxicogenomic services for drug discovery
	Curagen	2002		Expansion of agreement to evaluate potential toxicity of early stage compounds
Pfizer	Genaissance	2001		Access to HAP database for drug development
	Perlegen Sciences	2002	2.2 m $	License, research. Genetic contributions to cardio disease.
	ViroLogic	2002		Development, license, research. PhenoSense HIV, GeneSeq, PhenoSenseGT and PhenoScreen.
	CuraGen	2003		Collaboration, license, research. Toxicogenomic & drug pathway mapping technologies.
	CXR Biosciences	2003		Research. *In vitro* assays to characterise metabolism of a class of compounds.
	First Genetic Trust	2003		FGT to design a strategic genetic banking system for Pfizer using enTRUST technology
	Perlegen Sciences	2004		Collaboration, license, research. Metabolic Syndrome research.
	Perlegen Sciences	2004		Collaboration, license. Major Depression Disorder treatment.
	The Brain Resource Company			Pharmacogenetic services in clinical trials.
ParkeDavis	Sequana	1997	103 m $	Genomics for schizophrenia and bipolar disorder

Company (Buyers)	Partner (Sellers)	Date	Deal size	Recap categories / description
Pharmacia	Genset	1998		Identification of genedrug response associations (pre/ clinical) efficacy
	Epidauros	2001		PGx testing for clinical development – screening trial participants
	Myriad	2001		Pharmacogenomics research collaboration – association study
	deCODE Genetics	2002		Patient stratification in clinical trials of CV disease
WarnerLambert	Third Wave	1999		PGx assays
Proctor and Gamble	CXR Biosciences	2003		License. HRN mouse technology.
Roche	deCODE Genetics	1998	200 m $	Gene discovery and pharmacogenomics
	Affymetrix	2003	70 m $	License. GeneChip® technology for diagnostics.
	Epigenomics	2003	105 m $	Collaboration, license. Diagnostic products for early cancer detection.
Roche Molecular Sciences	Affymetrix	1998		Development of diagnostic tests for HIV genotype
	Epidauros Biotechnologie	2003		License. Polymorphism in the CYP2D6 gene.
Roche Diagnostics	Millennium Predictive Medicine	2000		Development of diagnostics to guide prescribing (RA)
	deCODE Genetics	2001	300 m $	Development of DNA diagnostics, PGx tests and point of care products
Sankyo Pharma	Gentris	2003		Collaboration, license, research. Pharmacogenomic alliance
Sanofi Syntholabo	Genset	2000		Identification of genedrug response associations (discovery)
Schering AG, Berlex	Phase1 Molecular Toxicology	2000		Collaboration. Toxicological screening on preclinical candidates
Schering Plough	Oncormed (now Gene Logic)	1997		P53 gene therapy – variant/ response association study (gene therapy)
Serono	Genset	2002	106.4 m $	Acquisition. Acquisition for cash
Sumitomo Pharmaceuticals	Gene Logic	2004		License. Access to BioExpress System, ASCENTA System and ToxScreen reports.
Wyeth	deCODE Genetics	2002		Gene expression data in clinical trials of drug for respiratory disease
	Epigenomics	2003		Collaboration, license. Murine xenograft model in drug response marker studies.
WyethAyerst	Axys	1998		Role of CYP polymorphisms in metabolism of two classes of marketed drugs

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