

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

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>.

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the USA, with the remaining 40% in Europe (as a percentage of the number of companies with PGx-related activities, not of their financial market share).

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 particular 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**
 - Availability of DNA samples from well-characterised patients.

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- Lack of clear evidence to relate drug response (both safety and efficacy) to genetic status.
- 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. On the smaller markets of the Netherlands and Ireland, Roche was less active and the drive was generated by users, 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 no 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:** Societal issues do not pose a problem. 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.
- **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

² <http://www.fda.gov/cber/gdlns/pharmdtasub.pdf> accessed on 1.6.2005.

³ <http://www.fda.gov/cder/genomics/pharmacococonceptfn.pdf> accessed on 1.6.2005.

therapeutic combinations as the Agency does not have primary responsibility for diagnostics and its remit is limited to approval of therapeutics.

- 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:** Once 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.
- **Licensing of clinical laboratories:** There is wide variation between national approaches to licensing clinical testing services. In the USA and Germany diagnostic 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. 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.