Regulatory and Quality Assurance Frameworks for PGX: A Comparative Study of the US, EU and Four EU Member States

PART 3 OF AN ESTO STUDY ON PHARMACOGENETICS AND PHARMACOGENOMICS: STATE OF THE ART AND SOCIAL AND ECONOMIC IMPACTS

Authors:

MICHAEL M. HOPKINS (SPRU, UNIVERSITY OF SUSSEX)]
GRAHAM LEWIS (SATSU, UNIVERSITY OF YORK)
SYBYLLE GAISSER (FRAUNHOFER INSTITUTE)
JIM RYAN (CIRCA GROUP, DUBLIN)
CHRISTIEN ENZING (TNO INNOVATION POLICY GROUP, DELFT)
JULIANE HARTIG (FRAUNHOFER INSTITUTE)
WIENEKE VULLINGS (TNO INNOVATION POLICY GROUP, DELFT)
TONY FORDE (CIRCA GROUP, DUBLIN)

Technical Report EUR 22214 EN

European Commission
Directorate-General Joint Research Centre (http://www.jrc.cec.eu.int)
Institute for Prospective Technological Studies (http://www.jrc.es)

EUR 22214 EN
Luxembourg: Office for Official Publications of the European Communities

ISBN *(will follow)*

Printed in Spain

Acknowledgements

The authors of this report are grateful to the information obtained from all our anonymous interviewees, and various other sources. All were very generous with their time. We are also grateful to the numerous people who read draft chapters and commented on them, and especially to Prof. Sandy Thomas at the Nuffield Council on Bioethics for her invaluable advice. Thanks also to Cynthia Little helped with the final formatting and presentation of the report.

Acronyms

ACBI	Association of Clinical Biochemists of Ireland
ACCE	Analytic validity, Clinical validity, Clinical utility & associated Ethical, legal & social implications
ADR	Adverse Drug Reaction
A&E	Accident and Emergency
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	Dutch 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
CE	European Community (refers to CE mark)
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CISH	Chromogenic in situ hybridization
CKKL	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
CML	Chronic Myeloid Leukaemia
CMS	Centers for Medicare and Medicaid Services
CPA	Clinical Pathological 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	Dutch Board for Care Insurers
DBC	Dutch Diagnosis Treatment Combination
DH	UK Department of Health
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
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
FMWP	Federation of Biomedical Scientific Societies
GAIC	US Genetics and Insurance Committee
GBA	Gemeinsamer Bundesausschuss

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
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	Intellectural Property Rights
IPRG	Interdisciplinary Pharmacogenomic Review Group
ISO	International Standards Organisation
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
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	Dutch Society of Clinical Cytology
NVVP	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
PT	Proficiency Testing
PV	Pharmacovigilance
QA	Quality Assurance
QSR	Quality Systems Regulation
RGO	Dutch Council for Health Research
Rki	Robert-Koch-Institut, Germany

RSC	Risk Structure Compensation
RVZ	Dutch Council for Public Health and Health Care
SAGGT	Secretary's Advisory Group on Genetic Testing (US)
SHA	Strategic Health Authorities (UK)
SHI	Statutory Health Insurance
SKKP	Foundation for Quality Assessment Clinical Pathology
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
STT	Dutch Foundation Futures of Technologies
TPMT	Thiopurine s-methyltransferase
UKAS	UK Accreditation Service
UKGTN	UK Genetic Testing Network
VGDS	Voluntary Genomic Data Submission
VHI	Voluntary Health Insurance
Vhn	Society Histotechnique Netherlands (Working Group Immuno Histocyto Chemistry)
VSOP	Dutch Genetic Alliance
WGP	Dutch Medicines Pricing Act

Contents

Chapter 1 Introduction

Michael M. Hopkins, SPRU, University of Sussex

1.1 Objectives and scope

This report is Part 3 of the ESTO study on 'Pharmacogenetics and Pharmacogenomics: state of the art and social and economic impacts'. The objective of this report is to compare the regulatory regimes that govern the development and clinical application of pharmacogenetics and pharmacogenomics in the USA, EU and four EU member states (Germany, Ireland, the Netherlands and the UK). This study does not make policy recommendations, but focuses on highlighting important commonalities and differences in the structures that make up the regulatory regime, the progress made towards accommodating PGx within that regime, and the remaining challenges.

Part 1 of the ESTO study maps key actors, trends and outputs of academic and industrial research and development in the field of pharmacogenetics and pharmacogenomics. Part 2 focuses on the clinical impact in social and economic terms of two early exemplars of pharmacogenetics and pharmacogenomic applications.

The scientific and technical fields as well as the relevant regulatory infrastructures that are the subject of this report (Part 3 of the overall study) are rapidly changing and so in pursuit of the objectives, the definition of key terms has been purposely made broader than those often used by practitioners.

1.2 Pharmacogenetics and pharmacogenomics

The history of pharmacogenetics dates back to the 1950s. The term pharmacogenetics is generally associated with inheritance, for example Weinshilboum and Wong[1] define pharmacogenetics as 'the study of the role of inheritance in inter-individual variation in drug response'. The term pharmacogenomics emerged in the late 1990s and is often associated with industrial application of genomics in drug discovery.[2] While many have struggled to reach agreement on the precise meaning of the terms pharmacogenetics and pharmacogenomics,[3] here we use the term PGx to refer collectively to the science and

[1] Weinshilboum, R. and Wong, L. (2004) 'Pharmacogenomics: From bench to bedside' *Nature Reviews Drug Discovery* Vol.3 September 2004 pp. 739-748.

[2] Snedden, R. (1999) 'Pharmacogenetics Workshop Background paper' The Wellcome Trust. http://www.wellcome.ac.uk/assets/wtd003274.pdf

[3] For example see: Snedden, R. (1999) 'Pharmacogenetics Workshop Background paper' The Wellcome Trust. http://www.wellcome.ac.uk/assets/wtd003274.pdf; Lindpaintner, A. (2002) 'The impact of pharmacogenetics and pharmacogenomics on drug discovery'. *Nature Reviews Drug Discovery* Vol. 1, June, pp. 463-469; FDA (2002) Workshop on Pharmacogenetics/Pharmacogenomics in drug development and regulatory decision making' May 16-17th, University of Maryland

technologies associated with dividing patients or populations into groups on the basis of their likely therapeutic response using a test for genetic variation. We therefore include 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, we do not limit our definition of a genetic test to methods that rely on direct DNA analysis. Phenotypic tests based on protein, metabolite or other biomarkers such as immunohistochemistry (IHC) tests and other non-genetics based test methods are also included where they may be used to reveal an underlying genetic change relevant to the therapeutic decision making process. We also include both heritable and somatic change as relevant to the field of PGx.

1.3 The regulatory regime

This study concerns the regulatory regime surrounding PGx in specific regions. As the mechanisms for governance of PGx and related fields such as genetic testing are still developing, there are few legal requirements at the national or international level controlling their use. However pre-existing legislation, rules, and codes of practice, monitored by government and professional organisations (at the clinical, pharmacy or laboratory level) are often relevant to the application of PGx. A broad interpretation of regulation has therefore been applied here so as to provide policy makers with a wide ranging view of measures that can be used to positively influence the performance of PGx technology in society. Pragmatically this means the regulatory regime as described here includes a wide range of factors influencing: the development and licensing of products and services; laboratory practices in training of staff, quality control and quality assurance; clinical guidance on the use of PGx tests and the implications of their results, as well as wider legal frameworks such as those addressing genetic discrimination.

1.4 Case study methodology and structure

PGx has the potential to have an impact on both therapeutics and diagnostics in medical practice. This is described more fully in Part 1 and Part 2 of this ESTO study. These impacts are likely to be felt in drug development, drug approval and clinical use and may enable industry and medical practitioners to minimise adverse effects and improve therapeutic efficacy for both pre-existing and novel therapeutics. Each case study therefore follows the path from ‘research bench to bedside’ to review the regime in place at each point along the way.

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http://www.fda.gov/cder/genomics/presentations/Meeting_Workbook_10May02.pdf; Hedgecoe, A. (2004) *The Politics of Personalised Medicine – Pharmacogenetics in the Clinic Cambridge Studies in Society and the Life Sciences*, Cambridge University Press, Cambridge.

1.4.1 Country case studies:

The national case studies that make up Chapters 2, 5, 6, 7 and 8 are structured around the following main areas:

- *The national context including structure of healthcare provision and relevant institutions*

  An outline is provided to identify state and non-state actors (such as regulatory agencies, professional bodies, and patient groups) and system of healthcare provision that provides the context for the relevant legal frameworks and development and implementation of regulations within the case study nation.

- *A description of the current regulatory regime applied to PGx products and services*

  A description is provided of how the national drug and device regulatory agencies have adapted their frameworks to encompass the use of PGx, for example in clinical trials and licensing. The response of these agencies to EU Directive 98/79/EC on in vitro diagnostic medical devices, the US Food and Drug Administration (FDA) guidance on PGx and their experiences approving PGx products to date are also discussed here.

- *The clinical use of PGx testing*

  An analysis of the system of laboratory testing in support of clinical practice is provided for each national case study. This covers the local mechanisms controlling the introduction of tests, the oversight of laboratories, including accreditation and quality control processes as well as the laboratory/clinician interface.

- *Remaining challenges*

  A summary of the issues identified by national sources as problematic or of potential concern in the further development and application of PGx technologies, particularly those faced by regulatory agencies, clinical and laboratory professionals, is provided for each country.

Case studies were undertaken through use of a range of sources including web-based review of the relevant national institutions, literature reviews of key national publications on PGx and interviews with experts in the field.

In each country at least five, and in some cases more than ten interviews were conducted to gain a range of perspectives (including a government health policy perspective, a regulatory agency perspective, and a laboratory service perspective). Where possible multiple interviewees were sought from each perspective.

1.4.2 An assessment of EU level policy relevant to PGx

In addition to the five national case studies, this report examines EU level initiatives relevant to PGx through review of the policy literature and interviews with the European Medicines Agency (EMEA). These are reported in Chapter 3 which includes analysis of the EU regulatory regime for PGx, such as discussion of the In Vitro

Diagnostics (IVD) directive, progress and policies of the EMEA and the challenges that will have to be faced.

1.4.3 An industrial perspective

An industrial perspective was sought to provide international comparisons between the regulatory environments in the EU, USA, Japan and EU member states regulatory regimes through interview with 15 firms (see Table 1.1). The firms interviewed were asked in particular to comment on how US policies, as elaborated in the FDA's draft guidance (the interviews being conducted prior to the recently published 2005 FDA guidance) and EU policies such as the IVD directive and frameworks developed by the EMEA affect industry's development of PGx products.

Table 1.1: Companies Interviewed

Company	**Country of interviewee**	**Sector**
Abbott Laboratories	USA	Large Pharma
Astra Zeneca	UK	Large Pharma
DakoCytomation Denmark A/S	Denmark	Diagnostic/Bio-Pharma
DxS Ltd.	UK	Service
Epidauros Biotechnology AG	Germany	Service
Hoffmann-La Roche AG	Switzerland	Large Pharma
Genaissance Pharmaceuticals	USA	Diagnostic/ Service
GlaxoSmithKline	UK	Large Pharma
ICON plc	USA	Contract research Organisation
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
Wyeth Pharmaceuticals	USA	Large Pharma

Chapter 2 Regulatory frameworks for PGx in the USA

Michael M. Hopkins, SPRU, University of Sussex and Graham Lewis, SATSU, University of York

2. 1 US health care system structure and expectations of PGx

The US healthcare system is characterised by a multiplicity of provision systems with the majority of healthcare spending coming from private insurance schemes and healthcare management organisations. Nonetheless the federal government accounts for around 45% of healthcare spending with around 1 in 4 Americans benefiting from Medicare, Medicaid and the federal Children's Health Insurance programme – totalling $519 Bn or 20% of the federal budget.[4] The reimbursement decisions made by federal programmes aimed at regulating roducts or improving services are at the heart of the healthcare system within which PGx operates because the government is the single largest payor.

The three relevant government institutions involved in oversight of PGx are all part of the Department of Health and Human Services (DHHS). The FDA oversees drug and device licensing, including diagnostic test kits and reagents. The Centres for Disease Control (CDC) has a public health focus, and its Division of Laboratory Services develops guidelines and policies for diagnostic testing. The Centres for Medicare and Medicaid Services (CMMS) administers regulatory management of laboratory services and the reimbursement of those services provided by Medicaid and Medicare.

Policy on 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 Project.

The NIH-Department of Energy joint working party on ethical, legal and social implications of human genome research commissioned a report on the context of genetic testing in the USA in 1995. The report, which was published in 1998, highlighted the need for greater regulatory oversight of genetic testing services.[5] Following on from this study, in 1998, the Clinical Laboratory Improvement Advisory Committee (CLIAC), located in CDC, recommended that the Clinical Laboratory Improvements Act (CLIA – discussed in section 2.4) should be updated to establish a specific regulation to address genetic testing. In 1999, the DHHS Secretary's Advisory Group on Genetic Testing (SAGGT – formed on the recommendation of the Holtzman and Watson report of 1998) also called for greater oversight. However no new regulation has been agreed although CDC is currently developing new guidelines (see

[4] http://www.cms.hhs.gov/researchers/projects/APR/2004/facts.pdf

[5] Holtzman, N.A. and Watson, M.S. (eds) (1998) *Promoting Safe and Effective Genetic Testing in the United States. Final report of the task force on genetic testing*, Johns Hopkins University Press, Baltimore MD.

section 2.4 below).

2.1.1 Expectations of PGx

It is not necessary to look far for examples of high expectations surrounding pharmacogenetic testing in the USA even in 2004 and 2005. In particular those in policy circles promise significant change within a decade,[6] and even at the National Human Genome Research Institute, scenarios are discussed where pharmacogenetics can make a difference between an individual dying at 50 and living to well over 100.[7]

Hopes for personalised medicine are also being actively promoted in the USA by a lobby group known as the Personalized Medicine Coalition (PMC), although they are cautious in noting that these developments will take time:

> Personalized 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. Personalized 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.[8] It appears to be primarily industry driven, but has a broad membership, which includes representation of government agencies, universities, professional and industry associations, large pharma and biotech firms.[9] The views of the PMC appear to be echoed in DHHS advisory circles where there are also high hopes for PGx (Policy 2).

In the view of those at the forefront of research it is hard to tell the extent of the impact that PGx will have on healthcare in the USA, although it is thought that recent scientific and technical developments are promising (Research Lab 2). It is certainly felt to have large potential, although the time scales of early proponents are thought to be unrealistic and PGx introduction will take much longer than orginally anticipated (Research Lab

[6] 'During the next decade, the practice of medicine will change dramatically through genetically based diagnostic tests and personalized, 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

[7] http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf

[8] http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.asp

[9] 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.

1).

2.2 Regulation of medicinal products in the USA

The agency responsible for drug regulation in the United States is the FDA. The FDA consists of a number of centres, with the largest, CDER, responsible for ensuring the safety, efficacy and quality of medicines prior to marketing, and for clinical trials approval and 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 (IND) application. CDER also provides scientific and regulatory advice to sponsors during the drug development process, and the Agency as a whole engages in many other activities, including consumer education, research, and input into public policy on medicines and healthcare.

Marketed diagnostic tests are subject to regulatory review by the Office for In Vitro Diagnostics (OIVD), located within the Center for Devices and Radiological Health (CDRH) – in contrast to other countries where such extensive pre-market review is not 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 system of drug regulation evolved throughout the 20th century. The legislative foundation for US regulation is provided by the Food, Drug and Cosmetic (FD&C) Act of 1938, plus several important amendments. The most important of these are the Kefauver-Harris Amendments (1963), enacted following the thalidomide disaster, which introduced the requirement for proof of efficacy, control over clinical trials, and good manufacturing practices (GMP), and the Medical Device Amendment of 1976, which addressed issues of investigational use, registration, and GMP, based on a classification system for medical devices. The US Congress passed the Orphan Drug Act 1983 to provide incentives to companies to research and develop medicines for people who have disorders that affect fewer than 200,000 persons – so-called orphan drug legislation. The most powerful incentive introduced by the Act was marketing exclusivity.[10] According to several commentators, similar legislation may be necessary to encourage the equitable development of PGx technology.[11]

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

[10] 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, and help from the FDA in designing research protocols that will meet regulatory requirements, and tax credits.

[11] Pirmohamed, M. and Lewis, G. (2004) 'Implications of Pharmacogenetics and Pharmacogenomics for drug development and health care', in E. Mossialos, M. Mrazek and Walley, T. (eds) *Regulating the Cost and Use of Pharmaceuticals in Europe*, European Observatory on Healthcare Systems/WHO Europe, Maidenhead: Open University Press, pp 279-296. Webster, A., Martin, P., Lewis, G. and Smart, A. (2004) 'Integrating pharmacogenetics into society: In search of a model', *Nature Reviews Genetics*, Vol. 5, pp. 7-13.

pharmaceutical industry, signalling a shift to a 'user fee' structure in place of government funding for review activities. As part of this change, CDER agreed to phase in ambitious performance goals and new management policies, reviewing 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.[12] 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.

2.3 USA regulation of PGx products

2.3.1 Diagnostic devices

The MDUFMA introduced a number of significant features into 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.[13]

As described above, marketed diagnostics, including PGx tests, are subject to FDA review, whereas diagnostic tests developed by clinical laboratories – so called 'home brews' or 'lab-developed tests' (the term preferred by US commercial labs) are not subject to formal review by the Agency.[14] The sole regulatory framework applicable to tests provided through laboratories is compliance with standards laid down by the Clinical Laboratory Improvement Amendments (CLIA) regulations (see section 2.4 below). This dual approach to regulatory oversight of diagnostics has generated considerable debate, with manufacturers of marketed tests demanding the establishment of 'a level playing field' with regard to regulation. The US debate mirrors to some extent similar debates in the UK and elsewhere. For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has reportedly recently revised its approach with regard to regulatory review of 'in-house' tests in terms of application of the IVD Directive.[15] However, like elsewhere, in the US context the issues are complex, touching upon a range of topics including reimbursement, healthcare delivery and conflicting commercial interests, as well as regulatory science. Overall, the key feature with regard to diagnostics in the US context is the existence of pre-market review of marketed diagnostics, and the inevitable tension between this form of oversight and the

[12] Abraham, J. and Lewis, G. (2000) *Regulating Medicines in Europe: Competition, Expertise and Public Health*, London: Routledge.

[13] The MDUFMA also introduced inspections of device manufacturers by accredited persons (third-parties), under carefully prescribed conditions available at http://origin.www.fda.gov/cdrh/mdufma/mdufmasummary.html#1 Accessed 23/04/05.

[14] Clinical testing labs in the US are usually commercial operations, but a number of non-profit institutions, such as the Mayo Clinic, are also engaged in the provision of diagnostic services, including PGx tests.

[15] *ACB News* No. 496, August 2004, p. 4.

less interventionist approach to regulating tests provided by clinical labs.

2.3.2 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.[16] Essentially, a range of technological developments, including pharmacogenetics, is blurring the historical lines between the different FDA centres. 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'.[17]

In addition, the FDA has recognised criticisms regarding its 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.[18]

The OCP was established in 2002 to address these concerns, as required by the MDUFMA of 2002. The 2002 law gives the OCP 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 remains with one of the three product centres, CDER, CDRH, and CBER (Center for Biologics Evaluation and Research) to which they are assigned.

While it is likely that the OCP will play a co-ordinating role in the PGx approval process, the extent and nature of this involvement is unclear at this time.[19] However,

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[16] 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 stabilize the implants.

[17] http://www.fda.gov/oc/combination/overview.html Accessed 21/04/05.

[18] http://www.fda.gov/oc/combination/overview.html Accessed 21/04/05.

[19] 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

whilst the OCP operates within the legislative and institutional structures of US drug regulation, given an increasingly globalised pharmaceutical market and harmonised regulatory framework, many of the issues relevant to the management of combination products in the US are likely to be applicable to other regions including the EU. Interested readers are referred to the OCP website (www.fda.gov/oc/combination/) for more detail, and particularly to a survey of FDA staff in the three relevant centres (CDER, CDRH, and CBER) for perspectives on the issues and suggestions for improving the handling of such products.[20]

2.3.3 The use of PGx data in drug approval

The FDA shapes and moulds the drug approval process by interpreting and enforcing the legislative provisions laid down in the FD&C Act through the issuance of 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's approach to PGx.

The most important FDA guidance document to date with regard to PGx is the Guidance for Industry, Pharmacogenomics Data Submissions document, which after a series of drafts published over the past three years, was finally released in March 2005.[21] The Guidance document clarifies PGx data that are required to be submitted by industry, and those that are more exploratory which the Agency would like to be submitted under the agency's Voluntary Genomic Data Submission (VGDS) programme. Another important FDA document recently released is the Concept Paper on Co-Development.[22] This explores possible approaches to co-development and regulatory submission of data for approval of a drug and diagnostic – an area that remains uncharted in all regions. The FDA plans to publish a formal Guidance document on co-development by late 2005, based upon the contents of the draft Concept Paper and subsequent consultation process.[23]

According to a senior FDA/CDER source, PGx development and clinical adoption faces a number of scientific and non-scientific challenges. The main scientific challenge arises from the constraints imposed by limited scientific knowledge and, in particular, the lack of available tools to actually generate the type of information required. A second scientific constraint is the inability to generate such information in a reasonable amount of time. In addition, the complexity of the assays currently available is another obstacle.
The FDA believes that the Roche AmpliChip™ and similar technologies are likely to

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)

[20] http://www.fda.gov/oc/combination/perspectives.html

[21] FDA (2005) 'Guidance for Industry, Pharmacogenomic Data Submissions', US DHHS, FDA, CDER, CBER, CDRH, March. Available at http://www.fda.gov/cder/guidance/6400fnl.pdf Accessed 25/4/2005.

[22] FDA (2005) 'Drug-Diagnostic Co-development Concept Paper – Preliminary Draft', DHHS, FDA, April. Available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf Accessed 25/4/05.

[23] http://www.fda.gov/cder/genomics/whatsNew.htm Accessed 25/04/05.

help overcome these challenges by eventually providing both the type of knowledge and the degree of interpretation required to move the technology into clinical practice ('to the bedside'). Nonetheless, a huge amount of data will be generated and these need to be translated into useful information for the person who is prescribing, otherwise initiatives to encourage uptake will remain largely academic and never have a real impact on how drugs are prescribed.

Foremost among the non-scientific issues identified has been the lack of regulatory guidance on pharmacogenetic data. The agency hopes that the release of the PGx Guidance in March 2005 and establishment of the VGDS scheme will help overcome industry concerns about the FDA's intentions and its capacity to handle submissions containing PGx data. The FDA accepts that the lack of clear guidance with regard to pharmacogenomic data: 'generated an environment where sponsors really didn't know what was going to happen with the information that was submitted to the Agency' (FDA/CDER interview).

Equally important as written guidance is the programme of internal training to develop 'in-house' skills and expertise which has been underway for several months. Another important development has been the establishment of the Interdisciplinary Pharmacogenomic Review Group (IPRG), which brings together staff with an understanding of genomics who are distributed across the agency. Hitherto there has been no central place where genomic information could be reviewed within the agency. Taken together, the publication of the PGx Guidance document and formation of the IPRG, which will be responsible for assembling a team of scientists knowledgeable about genomics and therefore able to provide advice to assessors during the approval process, are viewed as a major step towards encouraging PGx development by providing the necessary review systems and building trust with industry.

As noted above, the FDA published its long awaited Concept Paper on co-development of drug and diagnostic tests in April 2005. The coordination of the drug-test protocol and learning how to combine development of a drug with development of the associated device is viewed by the agency as crucial to successful and timely approval of PGx products. The document addresses issues related to the development of in vitro diagnostics for mandatory use in decision making about drug selection for patients in clinical practice.[24] In the opinion of its authors, 'the parallel development of a drug and a diagnostic is a relatively new aspect of drug development which requires careful coordination'.[25] Previous examples suggest this has not been done very successfully in the past. Among the key issues highlighted are timing or 'when does what need to be submitted to which Center [i.e. CDER or CDRH]'. Communication within and between centres also probably needs to be enhanced, so that reviewers in different parts of the agency benefit from others' expertise and from better co-ordination of the overall review process.

The second area of concern, and one given considerable attention by the agency, is the question of biomarker definition and validation. The key questions here have been the

[24] FDA (2005) 'Drug-Diagnostic Co-development Concept Paper – Preliminary Draft', DHHS, FDA, April, p.2.
[25] FDA (2005) 'Drug-Diagnostic Co-development Concept Paper – Preliminary Draft', DHHS, FDA, April, p.5.

definition of what constitutes a biomarker, and how to define the difference between a known or probable biomarker, and an exploratory biomarker. The importance of these terms is that they define the type of data required to be submitted to the agency and data that are not mandatory, but may be voluntarily submitted under the VGDS scheme. In part, the current lack of clarity over the difference between 'probable' biomarker and 'exploratory' biomarker arises from tensions between the science and regulatory demands. However, although important, these definitional problems are considered minor obstacles compared to the challenge presented by the practical need to validate a 'probable biomarker' scientifically. In other words, sponsors must ensure 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.

A 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 compared to industry. Joint examination of case studies found that compared to industry, the FDA considered a lot more data to be 'voluntary' (i.e. exploratory in nature) rather than 'required data'.

Some observers have suggested that clinical trials data obtained from stratified populations might change the approach adopted by regulators towards those 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 hurdles for approval are not going to change. What will change is the time taken and the costs for the sponsor. In general, it is much easier to obtain approval if data from a stratified population shows efficacy in that population or group, compared to looking at the overall population. Oncology provides a particularly good example, because in cases where there is 10-15% efficacy demonstrated overall, the potential impact on development time and costs is huge if one is able to identify the responders to treatment and then run the trial in that sub-population.

One concern that has been expressed is the possibility that some section of the population will be excluded from targeted medicines – the so-called '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 interviewee 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 for drugs directed at unmet medical needs that exists in the US. For example, the 'unmet needs' criteria could be complied with by developing a drug for a sub-population identified as non-responders to a certain therapy and by doing so qualify for accelerated approval status, which offers a much more friendly regulatory environment.

2.3.4 Do regulatory frameworks encourage PGx in drug development?

With regard to existing regulatory frameworks, the FDA's intent is to encourage PGx development. The publication of the PGx guidance document and related guidances demonstrates this intent, as well as 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. There continues to be a certain amount of confusion and uncertainty within industry, but the hope within the FDA is that now that the guidance is published, industry concerns have been addressed. This does not mean that there are no legitimate questions outstanding or that none will arise in the future, because it is not possible to foresee all possible scenarios. But the FDA believes that the appropriate regulatory framework is now in place to enable such questions to be resolved as they arise.

One question that arises from adoption of the VGDS scheme is whether there would ever be circumstances where information submitted voluntarily could impact on the formal assessment process. Clearly, if regulators see a signal that points to a safety issue for example, they cannot ignore it, as to do so might constitute a significant disservice to public health. This is why the VGDS is called 'voluntary submission' because the onus is on the company to decide what to submit. However, to separate the two types of data review within the agency and to encourage trust on the part of industry, membership of the IPRG will be drawn from managerial level staff, who will ensure that individual reviewers of voluntarily submitted data will not be involved in subsequent formal review processes for the same entity.

2.3.5 A regulatory perspective on the expected impact of PGx

With regard to the future of PGx data in submissions, the expectation is that many more submissions will contain such data in the coming months and years if for no other reason than that 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 being developed by smaller companies also.

FDA views on the part PGx will play in pharmacovigilance (PV) are more circumspect. Our FDA interviewee suggested the issue can again best be examined in terms of its scientific and non-scientific aspects. With regard to the science, there will be difficult issues to resolve around the meaning of safety signals generated post market. Once a drug is approved and on the market, it has been decided that it is reasonably safe. However, marketing a drug is akin to a very much larger clinical trial and because of this there will inevitably be adverse events. But most of the time these are likely to be idiosyncratic and not foreseeable. Whether it is possible to develop tools that identify such people, and if this is possible, and whether it can be justified, are major question.

However, PGx will definitely play a role in PV, and expert systems are being set up to track the events and interrogate the signals. It may also be possible to go back and perhaps re-contact these people to see if they have some genetic profile that could be predictive of such an adverse event. In practice, the adoption of PGx post-marketing is likely to be decided on a case-by-case basis, according to the threat posed by the adverse event and the overall benefit/risk ratio of the drug in question.

The FDA is enabling the use of PGx in drug development through initiatives like the Pharmacogenomics Guidance document discussed above, and initiating the review of product labels of approved drugs in appropriate cases. There are no barriers to including PGx related information in labels. Herceptin is the best known example, but around 35% of US approved drugs have PGx information in the label.[26]

In legislative terms, if additional evidence is available, US federal law empowers the agency to describe this evidence and identify specific tests needed for the selection and monitoring of patients who need the drug.[27]

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 colectoral 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 has been changed to reflect the increased risk of neutropenia for individuals with the relevant genetic profile.[28]

2.4 Regulation of PGx diagnostic services – from the laboratory to the clinic

Formal regulation of diagnostic testing services is centred on legislation passed by the US congress in 1988 – the CLIA. The most recent CLIA regulations were published in February 1992 and are based on the complexity of the test method: thus the more complicated the test, the more stringent the requirements.[29]

CLIA specifies quality standards for proficiency testing (PT), patient test management, quality control, personnel qualifications and quality assurance (QA) for laboratories performing moderate and/or high complexity tests. Waived laboratories must enrol in

[26] Lesko, L. (2004) 'How Is FDA Enabling the Use of PGx in Drug Development and Product Labels of Approved Drugs?' Paper presented at Scientific American Targeted Medicine conference, 11 Nov. 2004, New York, NY, USA.

[27] Code of Federal Regulations, 21 CFR 201.57. Specific requirements on content and format of labeling for human prescription drugs (revised 2001).
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html Accessed 22/06/05.

[28] Lesko, L. (2004) 'How Is FDA Enabling the Use of PGx in Drug Development and Product Labels of Approved Drugs?' Paper presented at Scientific American Targeted Medicine conference, 11 Nov. 2004, New York, NY, USA.

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

CLIA, pay the applicable fee and follow manufacturers' instructions.[30] The CMS is charged with the 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 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 College of American Pathologists (CAP) also play an important role that influences the overall provision of testing services in the USA. Reimbursement arrangements and clinician and laboratory staffs' 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).

2.4.1 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 activity is viewed as part of the normal activities of the lab, as noted by one prominent pathologist in the CAP newsletter:

> many molecular labs do translational research. They run studies that use data derived from other lab's 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 rigor of CAP or CLIA guidelines to this translational research because it is not yet ready for prime time.[31]

Although not all the laboratories engaged in PGx interviewed were molecular genetics labs, they all were 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. This includes reference laboratories, often private, which provide a wide range of testing services, including tests for many rare conditions for clients over a wide geographic area, hospital based clinical laboratories, and university and hospital research laboratories. Yet there are not thought to be a great number of PGx tests being used in the USA at present (Policy 2).[32] Activity in the area of metabolic testing seems to be low apart from Cytochrome P450 and Thiopurine s-methyltransferase (TPMT) testing (Research Lab 1, 2, Lab 2). These tests have been termed the 'low hanging fruit', but 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

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

[31] Quoted from 'Keeping score: Daniel Farkas, PhD tracks the recent hits and misses in molecular testing' (Daniel Farkas, 2003) Feature story, April 2003, CAP Today – available at www.cpa.org/apps/docs/cap_today

[32] 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 HER-2, Cytochrome P450 and even terms such as 'pharmacogenetic' do not get any hits – accessed 16/04/05.

immunohistochemistry labs offering a service for HER-2, and Estrogen receptor (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, but there is a requirement for such reagents used for healthcare applications to be manufactured according to a Quality Systems Regulation (QSR) and for the laboratory to validate the performance of the assay in the population they intend 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.[33]

Because validation of new services is left to up to the laboratory, and there is no simple way of universally setting thresholds to ensure test results are valid for a given procedure, it remains an area of concern at present. However, CLIA guidance on the development of new tests does advise clearly set out guidelines to be followed for validation, and a professional body, guidelines published by the Clinical Laboratory Standards Institute (CLSI) (formally known as NCCLS) are often used by laboratories as a de facto standard for validation of new assays (Lab2, 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 requirements, following the standard or guideline becomes mandatory (CLSI FAQs).[34]

2.4.2 CLIA certification

Federal regulation of laboratories performing diagnostic tests is administered by the CMS, with CLIA certification forming the central part of the regime.[35]

Congress passed the CLIA with the intent of establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed.[36] Like other regulatory agencies in the US and Europe, CLIA is user fee funded and all costs of administering the program must be

[33] CDC interview; Mansfield, E. O'Leary T. and Gutman S. (2005) 'Food and Drug Administration Regulation of in Vitro Diagnostic Devices', *Journal of Molecular Diagnostics* Vol. 7, No. 1, pp2-7.

[34] http://www.clsi.org/Template.cfm?Section=FAQ

[35] CDC interview; Mansfield, E. O'Leary T. and Gutman S. (2005) 'Food and Drug Administration Regulation of in Vitro Diagnostic Devices', *Journal of Molecular Diagnostics* Vol. 7, No. 1, pp2-7.

[36] Under CLIA, a laboratory is defined as any facility that performs laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health.

covered by the regulated facilities, including certification and survey costs.[37]

Under the CLIA legislation, laboratories that provide testing services for use in healthcare must be CLIA certificated. However these guidelines are regarded as setting a minimum standard only, due in part to the federal nature of the USA 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). In practice this means that laboratories in one state must abide by rules made by other states, such as the New York State legislature, if they are to test patients from that jurisdiction. As a result they are visited for inspections even though they may be practising thousands of miles away (Lab 2).

With 185,000 CLIA certified laboratories, the CMS has awarded deemed status to organisations including the CAP to inspect laboratories on their behalf. Laboratories are inspected at two-year intervals and granted a CLIA licence if they pass. They are then able to perform the types of tests specified on their certificate. New tests can be added between inspections provided that the laboratory notifies the CMS and that the appropriate paperwork is provided for inspection when the laboratory is next inspected for certification. Laboratories are licensed to provide testing services that fall into three categories according to complexity, genetics being in the most stringent, with requirements for example to engage in proficiency testing and to hire only staff with particular skills (CDC).
If laboratories fail their proficiency test, they can have that service removed from their CLIA certificate and cannot ask for reimbursement from CMMS (Lab 2), but this does not affect their other services (CDC). Indeed One CLIA certificate is required per street address, so that a licence may cover many laboratories in one building (CDC).

If a laboratory loses its CLIA licence it may not provide testing services, however in theory it is difficult to prevent laboratories from disbanding and reforming under a new name, although named directors can be barred from running laboratories.

Physicians are not supposed to send samples to a laboratory without CLIA certification, but this does occur, especially in the area of rare genetic disease testing where often a research laboratory is the only location where a test is available. In such circumstances legal proceedings could be initiated, but the CMS generally would work with the laboratory to bring their practice into compliance by playing an educational role. Only if their advice is ignored would other steps be taken.

Without a CLIA certificate, federal reimbursement from CMS is not available for services, and this is a strong incentive to maintain performance (Lab 2). This point was noted by the CDC:

> 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).

Although perhaps not relevant to PGx tests, it is important to note that the CLIA system

[37] In practice there is a range of arrangements with regard to user-fees. The FDA and EMEA are partly funded by user fees; the UK MHRA is fully funded; and the Japanese agency is not user-fee funded.

is not the only federal inspection system, for example blood banks enjoy a more rigorous inspection regime with FDA and Association of American Blood Banks inspections) in addition to CLIA certification. It should also be noted that CAP accreditation (see below) does not ensure CLIA certification – it is possible to have one without the other (CDC).

The CLIA programme is not without its critics. Leaving aside the issue of commercial 'fairness' and marketed versus laboratory developed products (discussed in section 2.3 under diagnostic devices), complaints about CLIA typically focus on the frequency of inspection and the degree of transparency and independence within the compliance process.

Furthermore CLIA is not specific enough for full administration of genetic testing services and in May 2000 an effort began to develop a rule for a genetics speciality within the CLIA law with the publication of a Notice of Intent for public comment. This elicited around 800 responses.

Issues receiving the most comments following CDC's Notice of Intent

1. Definition and categories for genetic testing
2. Documenting clinical validity
3. Who should be authorised to order a genetic test
4. Documentation of informed consent
5. Laboratory providing consultation/ counselling
6. Pre- and post- analytical phase requirements
7. Personnel qualifications/responsibilities.

Source: Boone (2001).[38]

The process of change in guidelines is slow because these comments must be taken into account before the agencies negotiate to take the rule to congress.. This process has been known to take 7-10 years (CDC). In the meanwhile CDC is actively engaged in other projects to shape the way in which genetic testing services are delivered. These include the Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications (ACCE) project (recently concluded) and its successor the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project. ACCE aims to build a methodology to aid policy makers to evaluate genetic tests prior to their wide scale introduction. EGAPP is attempting to put the ACCE outputs together with previous advisory group recommendations and CDC findings into action to evaluate tests as they enter the clinic.

2.4.3 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

[38] Boone, D.J. (2001) The Role of CLIA in the Oversight of Genetic Testing, available at: www.phppo.cdc.gov/dls/genetics

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 US pricing system, perhaps surprisingly is not purely market led but follows CMS pricing policy, with private insurers mirroring CMS decisions (Policy 2). The reimbursement price is based on a calculation which breaks the test down into stages, each of which are given billing codes according to the Current Procedural Terminology (CPT) system devised by the American Medical Association. In this system a test is divided into processes such as a PCR reaction, a DNA extraction step, and so on. However, it is the CMS that sets the actual monetary value given to these tests. While much of the ground covered by genetic testing methodologies has cleared the way for PGx tests to be priced, it has been suggested that the reimbursement for the manual testing processes that PGx relies on may be too low although others indicate this may affect some labs more than others (discussed further in section 2.5).

No national decisions have been made by CMS regarding the reimbursement of PGx tests, although regional autonomy within the CMS allows reimbursement, based on existing published data (Research Lab 2). Given the early stage of PGx, private healthcare reimbursement is made on a case-by-case basis, often at the local level (Lab 3).

2.4.4 A central role for professional bodies

The CAP 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 as noted above the CAP has 'deemed status' and so can undertake CLIA certification inspections (as discussed above). Secondly it provides its own accreditation scheme. Finally, the CAP presides over a system of QA review known as PT.

2.4.5 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, not just laboratories)[39] and in a single accreditation process CAP accredited labs can meet the full spectrum of standards necessary for a lab to service the broadest patient population.

[39] see http://www.jcaho.org/about+us/index.htm

The CAP accreditation scheme is based on a peer-assessment system:

> Only the CAP utilizes working and experienced laboratory professionals in a peer-review inspection process. This approach provides your laboratory with inspectors who bring first-hand knowledge of the most current laboratory techniques and processes. Your laboratory will learn both from your own inspection as well as participating in an inspection of other laboratories (CAP website).[40]

Although other accreditation schemes exist (such as JCAHO, and American Society for Clinical Pathology (ASCP), the CAP appears to be the accreditation system of choice amongst the laboratories interviewed, although it is not a mandatory requirement across the USA.

The accreditation scheme covers all aspects of laboratory work ensuring protocols are followed for the following areas:

- Proficiency testing (see below)
- Quality control and quality management, (including supervision, record keeping, assay validation, requisitions, reporting, instruments, reagents etc.)
- Personnel (see below)
- Facilities
- Safety

Using a CAP check list for the relevant specialty,[41] a visiting team of inspectors observes laboratory practices as well as checking records, filing systems and protocols.

2.4.6 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 degree or masters. Technical staff also need to be qualified, although this can in theory be simply experience of working with the director of the laboratory (CAP molecular pathology checklist, version 12/29/2004).

2.4.7 Proficiency testing

CAP manage a wide range of proficiency testing schemes in the USA.[42] These are run by advisory boards including members with laboratory expertise in the specific area of proficiency being examined and often including some members from other schemes to ensure a degree of cross scheme learning and liaison (CDC, Lab 4).

[40] see http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/benefits.html
[41] see http://www.cap.org/apps/docs/laboratory_accreditation/checklists/checklistftp.html
[42] See http://www.cap.org/apps/docs/laboratory_accreditation/ptgraded.html updated November 2004.

Schemes are grouped together under disciplinary based resource committees – for example the Cell Markers committee oversees immunohistochemistry, while the Cytogenetics committee oversees fluorescence in situ hybridization (FISH) testing. Although pharmacogenetic testing is often perceived to be a molecular genetic activity (Lab 5, Policy 2) the model of coupling drug regimes with test results obviously has the potential to have an impact across disciplinary areas. This has led to complications in the organisation of at least one PGx PT scheme as multiple committees within the CAP have an interest in such schemes. Nonetheless these are seen as teething problems, due to the evolving nature of PGx and are expected to be resolved through cross-disciplinary collaborations at CAP (Lab 5). The resource committees are coordinated by a Council of Scientific Affairs, and they must present the case for a new scheme to this higher Council through a step process when the need for a new scheme has been clearly demonstrated (Lab 4).

Once a PT scheme is established, the system is based on the circulation of samples for testing by the scheme organisers, and results are reported back for assessment. PT schemes can be graded or educational. In an educational scheme, lab responses are compared with the consensus view and the scheme organisers help to educate the laboratory community as to how the most consistent results are being achieved. In a graded scheme, there is still an educational component, but failure to meet the standard set by the scheme organiser will result in the scheme organiser issuing that laboratory with a notice of poor performance. While CAP proficiency testing is not viewed as a direct form of regulation, if the laboratory has consistently poor performance in a graded PT scheme and does not address this problem it can lose its CLIA certification for that service (Lab 4).

There is relatively little CAP activity in terms of PT specifically for pharmacogenetic testing at present (Lab 4, Lab 5). The only PGx test with a proficiency test is the FISH HER-2 and this is not graded at present (Lab 4).[43] The FISH HER-2 scheme is run by the cytogenetics resources committee of the CAP. It was established after pilot studies in 1995 and 1996 and currently has around 150 labs participating for FISH testing.[44] There is pressure for the CAP to adopt more graded schemes, and users expect this to occur around 2007 (Lab 4).

Where CAP do not have services, laboratories can organise ad-hoc proficiency testing programmes, whereby they exchange samples between themselves. This is a strategy actively being explored by some groups working in pharmacogenetics where CAP has not established a scheme as yet, for example in areas such as TPMT and Cytochrome P450 testing. However, perhaps because it is early days, interest is still relatively low (research scientist 2) and practice is very variable between laboratories making comparative assessment difficult (Lab 5).

[43] See http://www.cap.org/apps/docs/laboratory_accreditation/ptgraded.html updated November 2004.

[44] Mascarello, J., Brothman, A., Davison, K., Dewald, G. Herrman, M. Candless, D., Park, J. Persons, D. Rao, K. Schneider, N. Vance, G. and Cooley, L. (2002) 'Proficiency testing for laboratories performing fluorescence in-situ hybridization with chromosome-specific DNA probes', *Arch. Pathol. Lab. Med.* Vol. 126, December, pp. 1458-1462.

These PT schemes have proved to be a good way of generating data to bring about agreement within a community of practitioners, and active collaboration between the committees involved in Immunohistochemistry (IHC) and FISH testing for HER-2, for example, have borne fruit in that the strengths and weakness of different technical approaches have been demonstrated.[45] Nonetheless even after several years of HER-2 testing there are still disputes over methodologies and some laboratories are concerned about the continued use of IHC 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 (Lab 1).

At the policy level concern was expressed in the mid-1990s about the flexibility of the PT system, however these do 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.[46]

There have been efforts at international co-operation on standards for laboratory testing services, but these have suffered as champions have come and gone (Lab 4). However at a personal level staff do interact with colleagues from Europe and they have a high regard for equivalent European schemes. In some cases it is felt that the depth and quality of interaction is richer in some the European schemes, although these are more expensive to run as the following quotes illustrate:

> it is a much more rigorous system and I'm sure their participants benefit tremendously from it (Lab 4).

> You know, pathology in the UK, in particular the QA programmes are far more rigorous than anything we have in the States (Lab 1).

2.4.8 The clinical use of PGx data

In the USA, medico-legal responsibility for interpreting test results correctly lies with the physician, but very few physicians have digested information on PGx in a way that allows them to use it in a proactive manner (Lab 3). Therefore clinical laboratory staff have had to embrace the role of educators to the physicians and finding ways to make

[45] See College of American Pathologists, Cell Markets and Cytogenetic Committees (2002) 'Clinical Laboratory Assays for HER-2/neu amplification and overexpression: quality assirance, standardization and proficiency testing', *Arch. Pathol. Lab. Med.*, Vol. 126, pp. 803-808.

[46] Holtzman, N.A. and Watson, M.S. (eds) (1998) *Promoting Safe and Effective Genetic Testing in the United States. Final report of the task force on genetic testing*, Johns Hopkins University Press, Baltimore MD.

this information available to physicians is 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 in some cases know less than patients who have undertaken some web research.

Multiple routes are expected to be necessary to achieve a level of physician awareness of PGx, with approaches such as direct mail, newsletter, and web-based information provision all being pursued by some advanced centres to get to their clinical users (Lab 2). The subject of how to better inform test users has become a focus at some forums such as the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (Lab 3).[47]

Some disciplinary professional bodies are involved in provision of discipline based courses and workshops for continuing medical education, such as the American Psychiatric Association and the American Association for Clinical Chemistry, may be provided by commercial organisations. The National Coalition for Health Professional Education in Genetics, a cross-disciplinary professional body established in 1996, also organises conferences and training schemes, some of which are focused on pharmacogenetics.[48] However, medical training in PGx is only available at a few medical schools such as Harvard and the Mayo Clinic it even then is limited by curriculum time pressures.

2.4.9 Pharmacogenetic exceptionalism?

It does not appear that those practising pharmacogenetic testing in the US at present are well rehearsed in the social and ethical debates that have been emerging elsewhere – or at least these were not noted. Laboratory staff thought that pharmacogenetics would not be used in the same way as genetic testing for inherited diseases, and so there is less concern about the ethical issues it raises (Lab 2). Ethical concerns are the subject of debate at PGx meetings, but it is thought to be too early to reach any conclusion on whether issues of concern in other areas of genetic testing will also cause concern in PGx testing.

2.5 Remaining challenges for the regulation of PGx

A number of challenges have been identified by stakeholders relating to the regulation of PGx. While some of these have been introduced in the previous sections, a more detailed examination of the remaining challenges for the regulation of PGx is provided here.

The PMC has been active in highlighting the remaining challenges to be addressed, but they suggest there are few entirely new issues raised by the technology:

> None of theses issues is unique to personalised medicine, government regulation

[47] See http://www.iatdmct.org/ accessed 16/04/05.
[48] See http://www.nchpeg.org accessed 16/04/05

> 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.[49]

Francis Collins at the National Human Genome Research Institute emphasises the need for clarity over the groups holding responsibility for assessing the PGx tests as and when they become available for clinical use.[50]

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 policy makers adopt a coherent integrated approach to the legal, financial, social and professional issues that encircle this debate.[51]

The above emphasises that there has been a lot of industry interest in pharmacogenetics, and it is likely that industry rather than government will be driving the diffusion 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 so PGx tests may be offered more widely than advisable by some private laboratories, and more 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 part 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 (albeit of 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 and more reliable, less complex tools are needed to generate data, both for clinical use and for research and development. In practical terms clinical labs are more financially restricted than those involved in industrial R&D, and as a result they rely on Single Nucleotide Polymorphism (SNP) detection rather than microarray analysis for the most part as 'the technology is not robust enough day to day to give us the same kind of results' (Research Lab2).

Adequate 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 genoptyping as the characteristics of populations differ. It is often very time consuming and increasingly expensive to provide marginal improvements in test performance and so there is a need for agreement on how rigorous requirements for such tests should be and which populations they should be validated in (Lab 2).

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[49] Munroe, J. (2004) 'The public policy issues of personalised medicine: Where do we go from here?' *Regulatory Affairs Focus*, September, pp. 21-23.

[50] http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf

[51] Munroe, J. (2004) 'The public policy issues of personalised medicine: Where do we go from here?' *Regulatory Affairs Focus*, September, pp. 21-23.

The translation from research to clinically useful information is also seen as a major challenge. For example it has been suggested 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).[52]

Challenges in the regulatory arena (as discussed in section 2.3) have included the lack of guidance for drug developers (although recent FDA initiatives may have addressed this); the need to build up internal competencies and form new ways of working; and the classification and validation of biomarkers also represents a technical challenge. On the other hand the stratification of populations in regard to drug use was not seen to be a challenge given the existing mechanisms for accelerated approval '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 how to evaluate genetic test results, and for them to know where to find reliable information on genetics 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 in some of the leading institutions there is already some training, although this is limited to 90 mins of teaching. It has been suggested that the solution will be the training of a new generation of doctors, but this could take a decade (Lab 2). The educational problem does not stop at doctors, as at present insurers are also having to make case-by-case judgements with little advice (Policy 1). This generally is done at the local level and makes seeking reimbursement a laborious process as the testing lab has to explain its procedure to each jurisdiction (Lab 3).

As PGx testing is a newly emerging area some tests such as for Cytochrome P450 do not have proficiency schemes established yet (Research 1, Lab 5). Even where schemes are established, such as for tests like HER-2 testing, there is concern that these do not have sufficient 'teeth' (Lab 1) 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 of data and their clinical use require understanding of both genotypic and phenotypic factors and as such what is thought of in the US as 'pharmacogenetics' is not a broad enough category. The field crosses several disciplinary boundaries and there is a danger as one lab person involved in QA said that 'we have a little turf issue here' (Lab 5). All these related activities need to be addressed by entities that co-operate and act in a co-ordinated manner. Existing QA schemes vary in strength from field to field (Lab 1), and overall the 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 you need patient tissue samples 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 they 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).

[52] see http://www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf

It is felt that in some areas such as HER-2 testing, mandatory application of certain analytical criteria would improve the overall quality of testing. However rigidities within the CAP system of oversight make this level of intervention politically difficult. For this reason it is thought that change is more likely to be driven by a backlash amongst service users (Lab 1).

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 may 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 reimbursement for genetic tests is also set at too low a level for most tests making it unattractive for laboratories to offer services. This pricing system reflects the fact that medical testing in the USA is not really a market system – the reimbursement levels paid by insurance firms mirror those set by the CMMS 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 so there is 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 were sufficient if the provider was testing at the appropriate volume to gain scale economies (Lab 3).
Changes to the CLIA system to incorporate genetic testing as a speciality are in progress, which would have some implications for some PGx tests. However their eventual adoption is not seen as being especially problematic: 'the challenge is to make sure that there's compliance with the requirements as we move ahead and I don't think that's going to be a major problem' (CDC).

Although there are limited tests available for PGx in the USA at present, there is already a case where one lab 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 so say.

2.6 Primary Sources:

Interviews were conducted with two members of the CDC and two further individuals with experience of genetic testing policy, two research scientists focusing on pharmacogenetics, five laboratories engaged in clinical services, including one active QA scheme administrator, and one prospective QA scheme administrator. Of the clinical laboratories, two are engaged in HER-2 testing, two in cytochrome P450 testing, one in TPMT testing and one in therapeutic drug monitoring only.

Chapter 3 EU frameworks for the regulation of PGx products

Graham Lewis, SATSU, University of York

3.1 Pharmacogenetics and the EU regulatory framework

In this chapter, we outline the EU regulatory framework, and discuss the current position of the EMEA with regard to the likely challenges and opportunities presented by pharmacogenetics. We also briefly detail products that involve PGx and that are currently authorised for marketing in the EU. The section concludes with a discussion of outstanding issues.

3.2 Drug regulation in the European Union

European medicines regulation is characterised by 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.[53]

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 undergone periodic review and adjustment 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 growing recognition on the other that newly emerging therapies and technologies such as pharmacogenetics may pose additional challenges for regulators.[54]

Applications for marketing authorisation (MA) for biotechnology products must go through the centralised procedure, with the route optional for other innovative products. Recent changes mean that from November 2005 the centralised procedure will become mandatory for products for certain specified indications (oncology, diabetes, HIV, and

[53] 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.

[54] 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.

genital diseases). The centralised procedure results in a European-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 whether or not to recommend authorisation.[55] 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 whilst 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 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.[56] Together, these three directives laid the foundations for a European-wide system of harmonised medicines regulation and a single Community-wide market in pharmaceuticals.[57]

In practice, however, implementation of mutual recognition was slow, and in 1995 a new structure was introduced.[58] This set maximum time limits for assessment and reduced the grounds for objection by member states. It also provided the two routes for authorising medicinal products: a new centralised procedure with applications made direct to a new Agency[59] – since April 2004 known as the European Medicines Agency

[55] In practice the process is of course is 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, or possible side effects, or other issues.

[56] Subsequent problems in implementing these directives were examined by the European Commission's Pharmaceutical Committee, set up by Directive 75/320/EEC.

[57] Abraham, J. and Lewis, G. (2000) *Regulating Medicines in Europe: Competition, Expertise and Public Health*, Routledge, London.

[58] The definitive collection of 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

[59] 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.

(although the acronym 'EMEA' remains) and a revised 'mutual recognition' procedure – formally termed the decentralised procedure, and applicable to the majority of conventional medicinal products.[60]

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.[61] Disputes between member states are resolved through binding arbitration by the CHMP. Since establishment of the decentralised procedure, a Mutual Recognition Facilitation Group (MRFG)[62] has also been set up by member states to help resolve problems between states, and to coordinate and facilitate the procedure.[63]

Some ten years after its establishment, the European regulatory framework is undergoing another round of changes, although the main features of the two approval routes outlined above remain broadly the same.[64] The principal new legislation comprises Regulation (EC) No 726/2004,[65] and Directive 2004/27/EC,[66] which amends Directive 2001/83/EC on the Community code relating to medicinal products for human use.[67]

Regulation (EC) No 726/2004 also extends the scope of the centralised procedure by making the procedure mandatory for orphan medicinal products and any medicinal product for human use containing an entirely new active substance (i.e. one that has not yet been authorised in the Community) and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes, with effect from 20 November 2005. With effect from May 2008, the centralised procedure will also be mandatory for medicinal products for human use containing a new active substance, and for which the therapeutic indication is for the

[60] Council Regulation (EEC) No 2309/936 and Directive 93/41/EEC.

[61] Applications are made to one member state (Reference Member State) which assesses the application and decides whether to approve 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.

[62] 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, and is 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).

[63] 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.

[64] EMEA (2005) 'EMEA Implementation of the New EU Pharmaceutical Legislation', available on line at: http://www.emea.eu.int/htms/general/direct/legislation/background.htm, accessed 25.05.05. European Commission (2005) 'European Commission Review of Pharmaceutical Legislation', available at: http://pharmacos.eudra.org/F2/review/index.htm, accessed 23.05.05.

[65] 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.

[66] 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.

[67] 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

treatment of auto-immune diseases and other immune dysfunctions and viral diseases.[68]

3.2.1 Regulation of in vitro diagnostics

Turning to the EU regulatory framework for in vitro diagnostics in the European context, as noted already, competency for medical devices resides with member states, with the primary legislation applicable to in vitro diagnostics at the European level being the IVD Directive (Directive 98/79/EC).[69] 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.[70]

The Directive introduced for the first time 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. In outline, 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 must 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 have until December 2005 to comply with the legislation. This arrangement meant that, during the five year transitional 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 to be placed on the market and from December 2005 only CE marked devices can be 'put into service'.[71]
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

[68] European Parliament (2005) 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).

[69] The *In Vitro* Diagnostic Medical Devices Directive (98/79/EC) was formally adopted in October 1998 and published in the Official Journal of European Communities on 7 December 1998 (OJ No. L331 7.12.98 p.1).

[70] Directive 98/79/EC was published December 1998. See Official Journal of the European Communities Ref.L331. The Directive provided for a 12 month period for transposition into national law, i.e. 7 Dec. 1999.

[71] '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'.

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 abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures'.[72,73] This definition makes it clear that an in vitro diagnostic medical device in the form of a pharmacogenetic test is covered by the Directive. Also, according to the Directive, the conformity assessment procedures apply not only to in vitro diagnostic medical devices which are placed on the market, but also 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).

Thus the provision of diagnostic services, such as 'home brews' would generally also need to comply with the appropriate conformity assessment procedure in respect of that device.

The overall purpose of the IVD Directive is to supplement the Community legal framework governing the conditions for the placing on the market of medical devices by extending legislation to include in vitro diagnostic medical devices. To help ensure that uniform Community rules develop, it has been broadly based on the provisions contained in 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 specimens derived from the human body.

Medical applications include analyses to assess a person's state of 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 with account being taken of their intended purpose, as well as in terms of the protection of users and third parties. In addition, it harmonises the conformity assessment procedures to be applied by manufacturers before they place devices on the market.

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[72] 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 21/06/05).

[73] 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 21/06/05).

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

For a whole range of in vitro diagnostic medical devices, with the exception of self-testing devices, Article 9, in conjunction with Annex III, of the Directive provides for checking of the design and manufacture on 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 primarily used 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' of Annex II of the Directive, the intervention of a notified body is needed before a device can be placed on the market. These are specific devices the accuracy of which is essential for medical practice and any malfunction of which is likely seriously to endanger health.[74,75]

3.2.2 Clinical Trials Directive

The other notable development relevant to PGx development is the Clinical Trials Directive (2001/20/EC),[76] which introduced additional responsibilities for regulatory authorities, and for ethics committees, and for those running or supporting clinical trials of medicinal products. The Directive was agreed in February 2001 and the final version published in May 2001.[77] Member states were given until May 2003 to draw up legislation implementing the Directive, although application of the requirements could be delayed until May 2004. The scope of the Directive is wide, covering the conduct of all clinical trials (CTs) in the EU on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC. The term 'medicinal product' under Directive 65/65/EEC turns on whether it is either medicinal by function, or is presented as treating or preventing disease in human beings. In effect, every clinical trial involving medicinal products will be covered, whoever sponsors it, whether industry, government, research council, charity or university.

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[74] 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 21/06/05).

[75] 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.

[76] The full title of the Directive is: 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. The text of the Directive is available at http://www.europa.eu.int/eur-lex/en/search/search_lif.html

[77] Official Journal of the European Communities (L121, 34-44).

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. In addition, it covers certain procedures for commencing a clinical trial. 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 with the exchange of information between member states, secure networks will be established linked to European databases for information about approved clinical trials and about pharmacovigilance. The Directive's provisions do not distinguish between commercial and non-commercial clinical trials (i.e. those conducted by academics without the participation of the pharmaceutical industry). However, non-interventional trials are not within the scope of the Directive, i.e. those where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation.

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

One of the concerns expressed has been whether introduction of the Clinical Trials Directive will impede the conduct of trials, and this concern has been voiced by academic researchers in particular.[78] If such criticism does have any validity, it is possible that the incorporation of academic research into broader PGx development may be hampered to some extent by the demands of the Directive, although whether this will be the case is currently an open question.

3.2.3 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 routes are utilised in practice is likely to be shaped by two factors: the extension of mandatory submission requirements for certain therapeutic areas,[79] and the fact that the proportion of products submitted to the centralised procedure is

[78] For example, the UK Academy of Medicine has criticised some of the demands in the Directive, including what are described 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).

[79] 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 for marketing authorisation applications with reference to Article 3 and Annex of Regulation (EC) No 726/2004. Draft. EMEA/180921/2005 (1 June).

increasing and this trend is expected to continue.[80]

3.2.4 EMEA views on the challenges and opportunities presented by PGx

The following sections present the positions and perspectives currently developing within the EMEA, and particularly within the recently established CHMP Pharmacogenetics Working Group (PGWP) discussed below, plus documentary sources.[81]

3.2.5 Building scientific capacity at the EMEA

One of the questions observers have raised with regard to PGx development is whether regulatory agencies are properly equipped in terms of expertise and understanding of the technical and social issues surrounding the technology. For example, a general characteristic of genetics-based research is the enormous complexity of the data and the problems presented by interpretation. 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 EMEA to increase their scientific capacity in this area by appointing additional expert staff recruited from academia. Agencies doing this include the FDA in 2004 and the EMEA in 2005. Other examples include the Chinese (with particular interest in PGx and traditional medicines), Taiwanese, and S. Korean agencies.

The EMEA has also established the CHMP PGWP composed of experts in medicinal product assessment of safety, efficacy and quality. The PGWP also has direct input from academics who are members.[82] The PGWP is also supported by specialists in different therapeutic domains who are called in to provide expert advice as and when required. At the time of 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 PG testing methods used in MAAs.

The Agency has made efforts to consult with both industry representatives and other government bodies at the 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 Enterprise) and industry. This activity builds on previous work on PGx at the Agency that started in 2000. The EMEA approach has been to hold workshops to identify needs and then to set about fulfilling them. In 2000 the Agency identified a series of needs that were addressed over the following four years. Developments included: establishment of a

[80] The addition of specific indications from Nov. 2005 to the list of products that must go through the centralised procedure can be expected to increase this trend.

[81] Due to ongoing discussions within the Agency at the time of interview, the staff member interviewed was not able to present the official view of the EMEA with regard to a number of the points discussed.

[82] These individuals are leading figures in academic departments of genetics, or possess special expertise in the field (EMEA interviewee).

PGx Expert Group, which was replaced by the PGWP in May 2005,[83] publication of the EMEA Working Paper on Terminology, and engaging in a number of international activities. A second workshop was held in late 2004.[84] Outputs from some of the activities relating to emerging technologies including PGx, are publicly available via the EMEA website.[85] The EMEA has also published a Discussion Paper on a proposed Road Map which will map out the future of the Agency, including a series of reforms and changes in internal structures and procedures, such as improving transparency and communications.[86] According to the EMEA, the Road Map has some points in common with the FDA's Critical Path Initiative,[87] which aims to bring about faster development of safe and efficacious new drugs through the development of new methods and procedures for assessment although its overall brief is wider.[88]

The most important challenges confronting the EMEA with regard to PGx development are viewed as being very much of the same type as other new science applications the Agency faces with respect to pharmaceuticals, although different in both quantity and, in some senses, nature. In the opinion of our 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.

According to some observers, however, the relationship between a drug and a diagnostic is potentially challenging in the European context 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 it should be emphasised that this is not the view of the EMEA.[89]
In addition, as noted in Chapter 2, potential scientific and regulatory challenges associated with the co-development of drug and diagnostic have been highlighted by the FDA in their recently published Concept Paper on the subject which argues that 'the parallel development of a drug and a diagnostic … calls for careful coordination.'[90]

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[83] PGWP membership is at: http://www.emea.eu.int/htms/general/contacts/CHMP.html The PGWP chair is Dr Abadie, Vice-President of the Scientific Committee, and the deputy chair is Prof. Flamiaon, both of whom are CHMP members.

[84] We were informed that the EMEA will probably publish the Proceedings of the Workshop, but this had not occurred at the time of writing.

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

[86] 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 25/05/05); EMEA (2005) 'EMEA Implementation of the New EU Pharmaceutical Legislation', available at: http://www.emea.eu.int/htms/general/direct/legislation/background.htm (accessed 25/05/05).

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

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

[89] See, for example, Webster, A., Martin, P., Lewis, G. and Smart, A. (2004) 'Integrating pharmacogenetics into society: In search of a model', *Nature Reviews Genetics*, Vol. 5, pp. 7-13, and Pirmohamed, M. and Lewis, G. (2004) 'Implications of Pharmacogenetics and pharmacogenomics for drug development and health care', in E. Mossialos, M. Mrazek and T. Walley (eds) *Regulating the Cost and Use of Pharmaceuticals in Europe* (European Observatory on Health Care Systems/WHO Europe), Open University Press, Maidenhead, pp. 279-296

[90] FDA (2005) 'Drug-Diagnostic Co-development Concept Paper – Preliminary Draft', DHHS, FDA, April. Available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed 25/4/05.

The EMEA has been supporting PGx development since 2002 with establishment of a dedicated expert group on PGx – the first by any authority. In early 2001 it began developing a new approach to emerging technologies, with an emphasis on support for development of focused drugs to improve public health. These activities were not fee-related (i.e. not user fee-based), but were supported by core funding on the grounds that this type of activity is an integral part of the Agency's brief.[91] According to the EMEA spokesperson:

> The initial impact on our decision making … together with the CHMP [has been]: is this new development of science likely to have a major role for the development of future medicines? And, if the Committee agrees, then the Agency invests in [a major way] to [develop] expertise which is able to cope with every aspect of these emerging technologies.

With regard to PGx, at this stage it is difficult to predict what and where the greatest impact will be. Nonetheless, the 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.' These changes 'will creep in gently, and they have already started creeping in [and] we expect big changes for certain types of treatment [but] not for everything' (EMEA interviewee).

The first challenge that confronted the EMEA was the internal one of scientific knowledge management. 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 to do this in each area (quality, efficacy and safety). To expedite the task of managing and disseminating this knowledge, the EMEA has appointed senior assessors of 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 upon scientific expertise and not representation, in contrast to EMEA Working Parties. As our interviewee described it:

> This complex working arrangement means that information has to come in [to the Agency], be digested, and then … distributed to the periphery. And this is the reason why we have to be cautious in going out with Guidance to the assessors, because we don't have the assessors all 'in house'. So you first have to educate them [and] try to stimulate their awareness, and their knowledge and understanding of the field. Only after that is at a reasonable state of maturity, can you then go ahead with [formal] Guidance.

[91] 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.

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 their files and by our assessors to ensure that the established criteria are adhered to' (EMEA Interviewee).

3.2.5.1 EMEA Briefing Meetings

Another important development was the establishment in 2002 of Briefing Meetings. These are meetings with individual sponsors outside the formal regulatory decision-making process and, with respect to 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 such as the development of diagnostic tests rather than drug development, or in some cases both, have requested such meetings across a range of therapeutic areas,.

As noted already, one area which has caused comment with regard to possible barriers to PGx development in Europe is the differences in approval structures for medicines and diagnostics. As described above, therapeutic agents are approved either centrally through the centralised procedure or by mutual recognition via the decentralised procedure. Both of these procedures can be viewed as 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.[92]

The EMEA believes that enactment of the IVD Directive presents the opportunity for developing a fair and equal approach to diagnostic approval across Europe rather than presenting additional barriers to development. However, as other observers have noted, 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, or how and what the purpose of a test is, for example, 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 likely to be a defining factor in clinical uptake.[93]
For these reasons, it is possible that the subject may need to be re-visited by the Commission in order to ensure that in the case 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 able to co-approve drugs and PGx tests. As the EMEA emphasised, the Agency does not examine diagnostic tests and does not seek to do so, and it does not envisage doing so in the future. If the need did arise the Agency would go to the Commission to discuss the issue, but at present it has had no need to do so.

[92] 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 resolving differences.
[93] Webster, A., Martin, P., Lewis, G. and Smart, A. (2004) 'Integrating pharmacogenetics into society: In search of a model', *Nature Reviews Genetics*, Vol. 5, pp. 7-13.

What might be an issue in the future, according to the EMEA, is the eventual need for a formal channel of communication on such matters between the national diagnostics authorities and the EMEA. For example, at the present time even the genomic tests for the anti-cancer agents Herceptin and Erbitux, are intended for diagnosis and not as a part of a package or kit comprising both drug and diagnostic. In the EMEA's view, we are moving to a situation where the diagnostic becomes a more sophisticated method for describing an indication for a drug. Thus in the case of the recently approved product, Erbitux, it is 'strongly recommended' in the SPC (Summary of Product Characteristics) that the test is used before treatment in order to identify those patients in which it is likely to be efficacious – in other words, the introduction of differentiation of disease based on a genomic test. EMEA competency extends 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 expressed 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 subject that is a global issue in the context of PGx and it has been suggested this may require further consideration by all regulatory agencies.[94]
Under current legislation the situation becomes much more complex if the test is used in a patient with a given genetic feature or marker. Marketing authorisation of a test linked to a product that segmented patients (i.e. rather than segmenting a disease) would only be considered 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 interviewee 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 interviewee).

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. In other words, not having clinical utility considered in the approval of diagnostic tests is a challenge that needs to be addressed. However the approval of a given test for a given drug is potentially problematic, especially if the products are manufactured by separate

[94] Pirmohamed, M. and Lewis, G. (2004) 'Implications of Pharmacogenetics and pharmacogenomics for drug development and health care', in E. Mossialos, M. Mrazek and T. Walley (eds) *Regulating the Cost and Use of Pharmaceuticals in Europe* (European Observatory on Health Care Systems/WHO Europe), Open University Press, Maidenhead, pp. 279-298.

firms and the companies are in disagreement 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 the mandatory use of a diagnostic test.

> What is important in Europe is that the criteria are the same, and then they can be implemented in any of the procedures available. So I don't see a major problem there [i.e. with regard to current approval routes] (EMEA interviewee).

In the European system, the approval route chosen is a decision for the sponsor. There is always a freedom of choice, except for the therapeutic areas where it will become mandatory to use the centralised procedure from November 2005 (oncology, diabetes, HIV, and genital diseases) which, it should be noted, are areas where PGx is more advanced.[95]

With regard to whether the existing regulatory framework encourages PGx development, although formal decisions have still to be taken, there is a belief that some changes will be required in existing rules and regulations. For example, there has been informal comment from Commission staff 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 what data should be included in relation to a PGx test, for example, or detail where in the document this should appear. Nor 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.

Changing the CTD may also present problems because the CTD is a product of the International Conference on Harmonisation of Technical Requirements (ICHTR) and any adjustment would require world-wide consultation and agreement by ICHTR members.[96] However, the overriding philosophy adopted by the Commission is that 'rules should not proceed the science' and that 'the rules should create a reference for science' and any that any changes must wait for the science to mature. Nonetheless, the EMEA, in consultation with the Commission, have 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.[97]

The Agency has also recently released the following guidance documents on PGx

[95] 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 criteria 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.

[96] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) comprising the regulatory authorities of Europe, Japan and the United States and the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration – see http://www.ich.org for details.

[97] 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 annex of regulation (EC) No 726/2004 EMEA/180921/2005 London, 1 June.

(http://www.emea.eu.int/htms/human/itf/itfguide.htm Accessed 06/05/05):

- Guideline on Pharmacognetics Briefing Meeting (released for external consultation 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.
- A Concept Paper on the Development of a Guideline on Biobanks Issues Relevant to Pharmacogenetics (Released for external consultation 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] and 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. Thus 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.[98]

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.[99]

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.[100]

With regard to voluntary submission of data via a Briefing Meeting, one difference between the US and European situations is that the FDA has elaborated the definition of 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

[98] http://www.emea.eu.int/htms/human/itf/itfintro.htm (Accessed 16/05/05).
[99] http://www.emea.eu.int/htms/human/itf/itfintro.htm (Accessed 16/05/05).
[100] EMEA (n/d) 'Emerging Therapies and Technologies', available at http://www.emea.eu.int/htms/human/itf/itfsupport.htm (accessed 16/05/05)

European level with a selected group of expert members of the PGWP.[101]

> So there will be no big consequences, because it's outside the formal procedure. Of course, if there is information exchanged that requires reflection on national procedures then the member states might call the company for clarification and further steps [...], but this is very unlikely to happen.

To date there have been about ten Briefing Meetings, and about fifteen case studies with real products in development have been discussed informally at such meetings.[102] A new development is that the EMEA and FDA are now holding joint Briefing Meetings with sponsors when requested to do so.[103]

3.2.5.2 PGx data and marketed products

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

Incentives to introduce such information do not exist. Whilst there may 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 so-called Article 31 legislation, which allows member states to request changes to the SPC and labelling of approved products if new data becomes available. This legislation may be applicable to new PGx data that becomes available, should a member state wish to invoke Article 31 for public health reasons in such circumstances.

In the US, the FDA is on record as expecting to re-review marketed products with a view to possible re-labelling if the application of PGx techniques, such as patient genotyping prior to treatment, leads to documented efficacy improvements or reduces serious toxicity. An example where this has already occurred in the US is the anti-cancer agent, irinotecan (Camptosar, Pfizer) which has had its label changed to reflect PGx information collected following approval.[104] Some patients treated with the drug suffer severe and prolonged neutropenia and the incidence of this side effect has a genetic component. The drug is available in Europe and was registered through the decentralised system (see below). Recent work has shown there is a genetic variant of

[101] Briefing Meetings are informal meetings in the sense that they are not part of the formal process of obtaining MA for a product.

[102] There is reportedly one case that was discontinued, but this product was later discovered to be identical to another one being developed.

[103] FDA (2004) 'Confidentiality arrangements concluded between the EU (EC and EMEA) and the US FDA/DHHS. Implementation Plan for Medicinal Products for Human Use'. Finalized. September 16, 2004

[104] FDA (2005c) 'Letter to Pfizer Inc. dated 7 June 2005. [with regard to supplemental new drug application dated March 30, 2005, received April 1, 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 22/06/05).

an enzyme involved in the metabolism of the drug which is associated with a very significant statistical increase in the risk of neutropenia.[105]

Re-labelling in the US has been the outcome of significant additional work by the manufacturer, Pfizer, with the FDA Advisory Committee strongly recommending the use of the relevant test in order to minimise risk of neutropenia and, in particular, its duration. The EMEA is in contact with FDA colleagues regarding 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. The irinotecan case may be the first example where a PGx test is the most powerful tool to significantly reduce a major toxicity problem that cannot be prevented by reducing the dose or by other means. Another possible example where re-labelling may 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.[106]

3.2.5.3 Submission of PGx data as part of a Marketing Authorisation Application

One issue likely to confront 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 either considered helpful, or even 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 developed products complete with clinical data. In such circumstances it is difficult to envisage demanding additional information unless there is specific evidence of serious negative effects, such as important safety issues or lack of efficacy for a cluster 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, one can envisage circumstances where a company was advised to undertake PGx studies during the Scientific Advice process in order to facilitate eventual approval.

3.2.5.4 Labelling of PGx products

As already noted, the EMEA expects PGx technology will impose changes concerning

[105] Another side effect of the drug is diarrhoea, a less severe side effect for the patient.

[106] Current PGx studies on warfarin include a major prospective study involving 2400 secondary and primary care patients in the UK (Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A., Walley, T., Farrar, K., Park, B. and Reckenridge, A. (2004) 'Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18820 patients', *British Medical Journal*, Vol. 329, July, pp. 15-19). A proposed FDA-sponsored prospective study on PGx and warfarin is expected to commence shortly (Interviews with FDA spokesperson, April 2005).

the legal framework, such as the format of data in the MAA. Labelling of a PGx product and its related diagnostic test is another area which is likely to 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.[107] In other words, at present the label is constructed in a somewhat ad hoc way. 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 demonstrated by the irinotecan example in the US. How such information is positioned on the label will also require clarification.

In many cases, PGx test are likely to be provided by commercial labs, and provision of these services may also require attention, with the creation of European-wide standards for QA to guarantee the quality and accuracy of all genetics-related testing across the community. However, currently 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 undertaken by commercial laboratories. At present, the EMEA is not qualified to intervene in such situations.

In the view of the Agency, however, any tension that might have emerged because diagnostics are approved at the national level and drugs at the EU level has dissolved because invited experts from national agencies responsible for approving diagnostic tests 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 expressed 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, there is the expectation that the EMEA will contribute to assessment of the diagnostic component of a 'PGx product' in term of clinical relevance and utility of the test to integrate the specification and the information on both drug and diagnostic, and that this will be done in collaboration with national authorities.

3.2.5.5 EMEA and emerging therapies and technologies

The EMEA has 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

[107] EMEA (2004) 'EPAR Erbitux Abstract', available online at: http://www.emea.eu.int/humandocs/Humans/EPAR/erbitux/erbitux.htm. (Accessed 16/05/05). 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 26/05/05).

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'.[108]

To this end, the EMEA has recently established a number of scientific committees, working parties and expert groups to contribute to the provision of scientific information in these areas. One of these – the EMEA Innovation Task Force (ITF) – was recently created to ensure EMEA-wide coordination of scientific and regulatory expertise and to provide a forum for early dialogue with applicants. As intimated elsewhere, this development appears to parallel developments in the US such as the establishment of the FDA's Interdisciplinary Pharmacogenomics Review Group (IPRG) and the Voluntary Genomic Data Submission (VGDS) scheme, discussed elsewhere in this report, although it is important to note that it not possible to judge exactly 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.

As already discussed, 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 at the EMEA. The briefing meetings are similar in some ways to the FDA voluntary data submission scheme (VGDS),[109] although it is unclear at this stage whether the EMEA intends to examine submitted data to the degree envisaged by the FDA, or commit similar resources.

As well as establishing the ITF, the Agency has sought to clarify the purpose and structure of Briefing Meetings. Thus 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.[110]

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.[111]

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

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[108] http://www.emea.eu.int/htms/human/itf/itfintro.htm, accessed 16/05/05.

[109] 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 16/05/05.

[110] http://www.emea.eu.int/htms/human/itf/itfintro.htm Accessed 16/05/05.

[111] http://www.emea.eu.int/htms/human/itf/itfintro.htm. Accessed 16/05/05.

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.'[112]

3.2.6 Products authorised for use in Europe

There are three products based on pharmacogenetics currently licensed for use in the EU, Herceptin (trasuzumab), Glivec (imatinib mesilate), and Erbitux. In addition, the author believes it is reasonable to assume that consideration is currently being given by the EMEA to re-labelling the colorectoral cancer treatment, irinotecan (Camptosar, Pfizer) following post-approval research which shows the benefits of patient genotyping, and the FDA's decision to include these findings in the US label. There are also some PGx diagnostic tests in clinical practice that determine genetic variation prior to treatment decisions for generic products, with TPMT testing prior to use of 6-mercaptopurine for childhood leukaemia being the best known, which is used as a case study elsewhere in this report.

3.2.6.1 Herceptin

Herceptin (trasuzumab) is a humanised monoclonal antibody that binds to the transmembrane protein related to the epidermal growth factor receptor (HER-2). It has been shown to inhibit the proliferation of human tumour cells that over express HER-2. Herceptin is approved for patients with metastatic breast cancer whose tumours over express HER-2.[113] HER-2 over-expression has been linked with a poorer outcome in patients with breast cancer. Consequently, HER-2 over-expressing breast cancer presents an ideal opportunity to exploit the concept of 'targeted' cancer therapy. The Marketing Authorisation (MA) for Herceptin was granted to Roche in August 2000, based on adoption of the assessment report by the CPMP in May 2000.

In the USA, where the licence holder is Genentech, the drug was approved in September 1998.[114] According to US sources, approximately 35,000 women in the US have been given Herceptin since FDA approval.[115] EMEA sources suggest around 25,000 users worldwide. The level of European use alone is not known although it has been available for several years in most EU states.[116]

HER-2 protein over expression is observed in 25%-30% of primary breast cancers.

[112] http://www.emea.eu.int/htms/human/itf/itfsupport.htm Accessed 16/05/05.

[113] Herceptin is indicated for use either as mono-therapy for patients who have received at least two chemotherapy regimes, or in combination with paclitaxel (Taxol) for treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable (EMEA, Committee on Proprietary Medicinal Products EPAR, Herceptin. Abstract. CPMP/1774/00, available online at http://www.emea.eu.int/humandocs/Humans/EPAR/herceptin/herceptin.htm).

[114] The FDA Center for Biologics Evaluation and Review (CBER) granted fast track and priority review status to Genentech's application for Herceptin and reviewed and approved it in approximately 4.5 months.

[115] Source: http://imaginis.com/breasthealth/herceptin.asp (Accessed 16/05/05).

[116] In the UK, wide-scale use was delayed until 2002 pending approval by NICE for NHS use.

Detection of this over expression is necessary for selecting patients suitable for treatment with Herceptin. Over expression is determined by one or more diagnostic tests, which are based on immunohistochemistry, or gene amplification using FISH of fixed tumour blocks. Whilst treatment rewards have been convincingly demonstrated, there remain a number of difficulties with regard to definitive conclusions about the benefits of Herceptin therapy for different patients, based on the FISH test.[117] The normal practice is to analyse tumour material using the IHC test, using the FISH test as a follow-up for ambiguous cases.

The CHMP updated the SPC for Herceptin with reference to diagnostic test methods to determine HER-2 status subsequent to initial approval. The diagnosis of HER-2 expression in the pivotal trials was performed using in-house investigational assays. In parallel with clinical development, a commercial assay was developed by DAKO, the HercepTest (DakoCytomation). In the meantime diagnostic developments continued and led to the introduction of HER-2 testing methodologies based on the detection of HER-2 gene amplification which is the initial genetic event that results in HER-2 over expression. FISH and CISH assays were developed and validated against IHC.

The SPC for Herceptin was updated in order to reflect the progress in diagnostic methods to determine the HER-2 status of a patient (previously defined on the basis of an IHC assay. FISH and CISH were included as an alternative to IHC to assess the eligibility of metastatic breast cancer patients for Herceptin therapy.[118]

The on-going scientific discussion is reflected in the current SPC by including in the indication section that Herceptin should only be used in patients whose tumours have either HER-2 over expression or HER-2 gene amplification as determined by an accurate and validated assay and refers to guidance on how to determine this. In the CHMP's view, the guidance is strict enough to preclude use of this drug in patients with insufficient HER-2 expression, since the risk-benefit ratio for these patients is critical due to considerable possible side effects of the drug. Guidelines have been developed for standardised, well-controlled procedures for the provision of reliable HER-2 test results, such as those in the UK, where a group of three reference laboratories was established to provide advice, QA, and materials where needed in the early years of HER-2 use.[119]

3.2.6.2 Glivec

Glivec (imatinib mesilate)[120] was developed by Novartis and authorised for use in the EU in November 2001 for treatment of chronic myeloid leukaemia (CML) in chronic phase after treatment with alpha-interferon, or in accelerated phases or blast crises,

[117] On this, and other information on Herceptin use, see, for example, information provided by Genentech, the US license holder, at: http://www.herceptin.com/herceptin/physician/pi.htm

[118] CHMP (2005) 'Herceptin EPAR Scientific Discussion', p37. Available online at: http://www.emea.eu.int/humandocs/PDFs/EPAR/Herceptin/177400en6.pdf Accessed 26/05/05.

[119] Ellis, I.O., Dowsett, M., Bartlett, J., Walker, R., Cooke, T., Gullick, W., Gusterson, B., Mallon, E. and Lee, P.B. (2000) 'Recommendations for HER-2 testing in the UK' *J. of Clinical Pathology* Vol. 53, 12, pp. 890-892.

[120] Glivec is known as Gleevec in the USA.

based on the assessment report and favourable opinion adopted by the CHMP earlier that year. The FDA also granted approval in late 2001, and regular approval in 2003, meaning the FDA has determined that Glivec has demonstrated a long-term clinical benefit for refractory CML patients. When originally approved in the US under the accelerated approval programme in May 2001, available evidence indicated that a long-term clinical benefit was highly likely, but further studies were necessary to confirm it. In Europe, the product was also approved for treatment of malignant gastrointestinal stromal tumours (GIST) in February 2002 and authorised by the Commission in May 2002. Glivec was authorised as an orphan medicinal product in February 2001 for the CML indication in Europe, USA and Japan.[121]

3.2.6.3 Erbitux

Erbitux (cetuximab) is used to treat patients with advanced colorectal cancer that has spread to other parts of the body.[122] Erbitux is a genetically engineered version of a mouse antibody that contains both human and mouse components. This new monoclonal antibody is believed to work by targeting the epidermal growth factor receptors (EGFR) on the surface of cancer cells, interfering with their growth. The product, developed jointly by Merck KGaA and ImClone Systems Incorporated/Bristol-Myers Squibb for the treatment of several types of human cancer that express the EGFR, was authorised in the EU via the centralised procedure in 2004 for use in combination with irinotecan for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.[123] Erbitux is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone for patients who cannot tolerate irinotecan.
In the data submitted for EU approval, a diagnostic assay (EGFR pharmDx) was used for immunohistochemical detection of EGFR expression in tumour material. A tumour was considered to be EGFR-positive, if one stained cell could be identified. Approximately 80% of the patients with metastatic colorectal cancer screened for clinical studies had an EGFR-expressing tumour and were therefore considered eligible for cetuximab treatment. The efficacy and safety of cetuximab have not been documented in EGFR-negative tumours.[124]

US approval was agreed in February 2004, and the FDA also approved a test kit to analyse a colon tissue sample.[125] The kit detects a protein in the body (HER-1) that

[121] EMEA (2001) 'EPAR Abstract, Glivec', CPMP/2418/01 Available online at: http://www.emea.eu.int/humandocs/Humans/EPAR/glivec/glivec.htm (Accessed 15/05/05).
[122] Colorectal cancer is the third most commonly diagnosed cancer worldwide, with an estimated 950,000 new cases diagnosed per year, and is the second most common cause of cancer mortality in Europe and North America. About 280,000 new cases and 150,000 deaths are expected in the European Economic Area including the enlarged EU, based on projected estimates for the year 2005.
[123] EMEA (2004) 'EPAR Erbitux Abstract', available online at: http://www.emea.eu.int/humandocs/Humans/EPAR/erbitux/erbitux.htm. Accessed 16/05/05.
[124] 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 26/05/05.
[125] The Erbitux diagnostic test is manufactured by DakoCytomation California, Inc., a subsidiary of Dako AS, Denmark.

stimulates cancerous tissue cell growth. Presence of this protein indicates that a patient is eligible for colon cancer treatment with Erbitux. In the US case, Erbitux was approved under the FDA's accelerated approval programme, which allows FDA to approve products for cancer and other serious or life-threatening diseases based on early evidence of a product's effectiveness. Although treatment with Erbitux has not been shown to extend patients' lives, it was shown to shrink tumours in some patients and delay tumour growth, especially when used as a combination treatment.[126]

3.3 Challenges raised by PGx from the EU-level perspective

The EMEA has undertaken a series of actions to prepare for PGx, including increasing the scientific capacity available to the Agency and the introduction of knowledge management activities.

According to the EMEA, there are no specific challenges related to the introduction of 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 upon cell and gene therapy and tissue engineering (EMEA interviewee).

Claims made by some observers that differences in legislative frameworks for drug and diagnostics approval may potentially present problems in terms of PGx development and clinical introduction in the European context were dismissed by the EMEA. In the opinion of the EMEA, the IVD directive will resolve any potential difficulties that emerge over the coming years with regard to separation of responsibilities for drugs and diagnostics between the European and member states 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 the 'careful coordination' of the parallel development of a drug and a diagnostic.[127] Based on the evidence provided for this study, how such development will be co-ordinated in the context of the EMEA and the European regulatory model, with its different legislative frameworks, is not yet clear.

[126] FDA (2004) 'FDA Approves Erbitux for Colorectal Cancer', press release, available online at http://www.fda.gov/bbs/topics/NEWS/2004/NEW01024.html Accessed 16/05/05.

[127] FDA (2005) 'Drug-Diagnostic Co-development Concept Paper – Preliminary Draft', DHHS, FDA, April, available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed 25/4/05.

Chapter 4 Industry View on Regulatory issues associated with PGx

Jim Ryan, CIRCA Group, Dublin

4.1 Introduction

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.

The following points on regulatory issues were extracted from responses to a telephone survey of 16 industry representatives. The companies involved are listed in the table below. They are mainly EU and US pharmaceutical companies of varying sizes and ages; 2 diagnostic companies, and 4 service companies. Some of the companies are involved in more than one of these activities.

Table 4.1 Companies interviewed

Company	Country of interviewee	Sector
Abbott Laboratories	USA	Large Pharma
Astra Zeneca	UK	Large Pharma
DakoCytomation Denmark A/S	Denmark	Diagnostic/Bio-Pharma
DxS Ltd.	UK	Service
Epidauros Biotechnology AG	Germany	Service
Hoffmann-La Roche AG	Switzerland	Large Pharma
Genaissance Pharmaceuticals	USA	Diagnostic/ Service
GlaxoSmithKline	UK	Large Pharma
ICON plc	USA	Contract research Organisation
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
Wyeth Pharmaceuticals	USA	Large Pharma

Within these firms, a senior executive with responsibility for pharmacogenetic activities was interviewed by telephone. Each interviewee was provided in advance with an outline of the study and the purpose of the interview. The persons interviewed occupied positions 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.

4.2 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 noted that a factor in their entry into PGx was a realisation that regulatory authorities would sooner or later start looking for pharmacogenetic data. However, even in their case, this was only one driver, but not the only one.

If regulatory compliance was a key driver, it would be expected that the PGx expertise would be located within the clinical development section of companies. This is not the case in the majority of pharma companies. In most of these, 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 of 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 be compiling genetic data on tissue samples. This is done so that retrospective genetic screening might be conducted in the event that differentiation of effect between patients was found in the trial process. In other companies, the PGx team was noted as being 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 4.1). Once again, none of these companies mentioned regulatory issues as a major reason behind client demand for their services.

4.3 Social/ethical barriers to use of PGx

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

4.4 Regulatory differences between EU, US and Japan.

Few respondents had experience of Japan. However, there was a clear view regarding differences between the EU and the US. These differences affected two aspects of companies' operations.

4.4.1 Samples and testing

No company had experienced any patient resistance to PGx products and none were expecting any difficulties in this area. The universal experience with patients has been that they have accepted the concept, and practice, of PGx drugs when it is explained to

them. Indeed, several companies noted the disconnect 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 was 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 requires companies to comply with a wide range of legislation. For practical purposes, this may mean that batches of samples from different EU countries must be treated differently in regard to 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 lot of complexity to a data handling process which is already very complex. It may, for instance be necessary to develop different array systems for samples from different countries because of variations in the data which it is permitted to collect from specific samples.

The 'constant discussion' on the need for further legislation also creates uncertainty about future data handling needs. Although companies were insistent that they would fully comply with all legislation, the diversity of EU requirements clearly presents difficulties that are not present in the USA (see also 4.4.2).

4.4.2 Regulatory differences between EU, US 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 in which to work than the US. In the words of one respondent, the EU is a 'logistical challenge' for pharma companies. The differences affected several aspects of company operations:

(a) Samples and Testing: The EU was almost unanimously regarded as a difficult area in which to conduct clinical research, and certain countries (e.g. Sweden, France) were cited on several occasions as examples. 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 noted that they were very willing to meet local legislation. The concern related to 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 seem to continually 'pop up' and that it was a 'pain in the neck' trying to constantly comply with the resulting procedural changes.

(b) EMEA and FDA: There was a majority view that the FDA had 'got its act together' in PGx drug regulation, and that they were pro-actively engaging with industry and others in defining a regime for approval of PGx drugs. FDA was seen as having actively organised meetings with relevant parties, including industry, to brief itself on the issues. It had then set about the process of defining guidelines for submission of data, again with extensive inputs from industry.

These guidelines have now been launched. EMEA, on the other hand, was seen as having lagged behind in this process and of not being internally as aware of the issues as FDA.

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

Comparative views of the two agencies included:
- 'FDA are more interested [than EMEA] in the science';
- EMEA are 'slower and more conservative than FDA'
- FDA are proactive and engaged with clinicians and industry. This was not felt to have occurred in EMEA as yet.
- FDA have been 'moderately enthusiastic' about PGx and has provided mechanisms to support data submission. (Respondent does not see the same attitude from EMEA.
- 'FDA are actively looking at the issues and staying abreast, whereas EMEA are 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 EMEA was about ethical issues rather than regulatory issues' whereas the FDA position on ethical issues was clear.

(c) 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 has consequences for the regulatory position in that regulatory authorities must engage with industry to understand current developments in the field. While FDA has done this, EMEA is reportedly less engaged. In addition, it is understood by the respondents that 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. While they 'know the science', they may not have a good appreciation of the practical issues surrounding drug development and approval.

(d) Diagnostics: Two diagnostic companies noted that the regulatory approach to their products was often very different between EU, US 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 may occur in any Dx product.

(e) Patents. One company noted that there was greater clarity in the US regarding the 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.

4.5 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 FDA and EMEA must engage so as to harmonise regulatory provisions, and were disappointed with the different rates of progress of the two agencies
- those who, while welcoming harmonisation, felt that it had a tendency to make the regulations less amenable to change. This group felt that it might not be useful to seek harmony 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.'

4.6 Regulatory 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 in the areas of sampling and biobanks. Several companies noted that final planning on their regulatory approach would not take place until they reviewed the regulatory guidelines which will 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.'

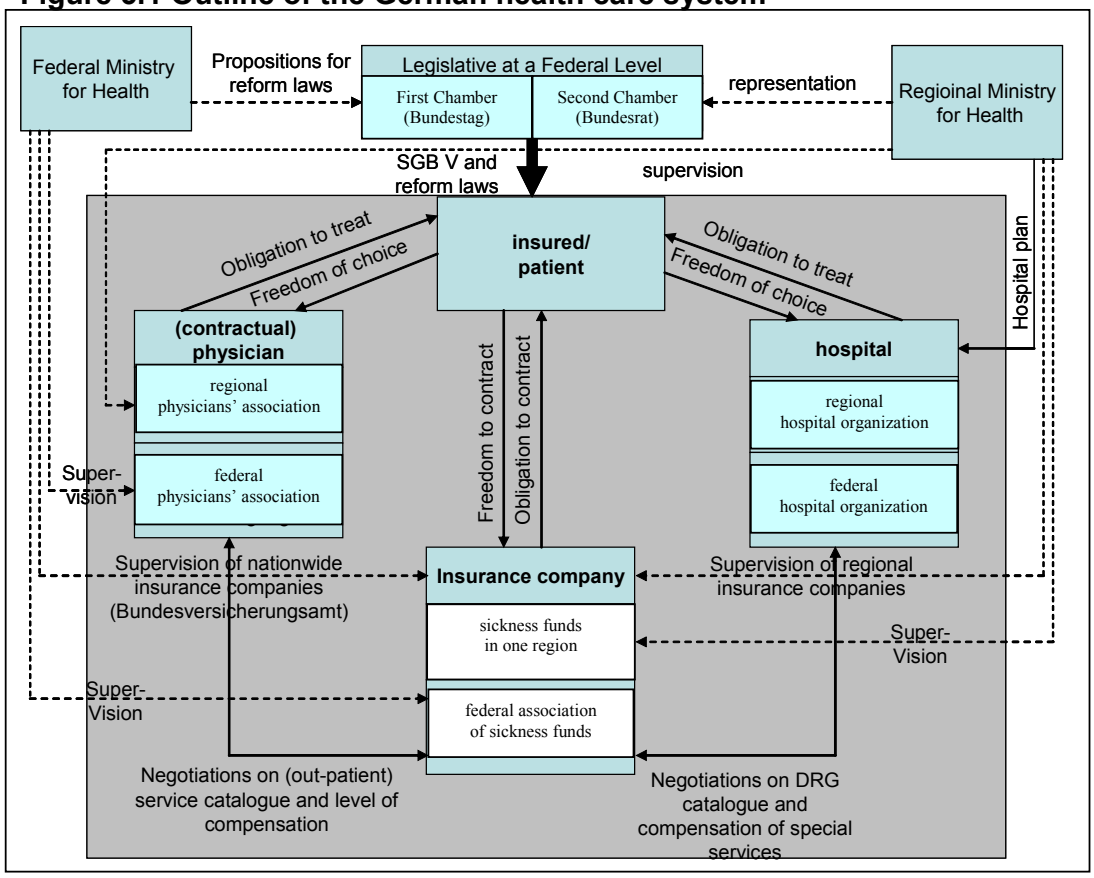
Chapter 5 Regulatory frameworks for PGx in Germany

Juliane Hartig and Sibylle Gaisser, Fraunhofer Institute

5. 1 Structure of the German health care system and expectations of PGx

Germany's health care system is characterised by a large amount of different actors. In the illustration (Figure 5.1) below, the main corner pillars are identified briefly.

Figure 5.1 Outline of the German health care system



Source: Busse (1990)[128]

As in other countries there exists a classical triad of prescription, consumption and payment among patients as demanders of health care services, health care providers as

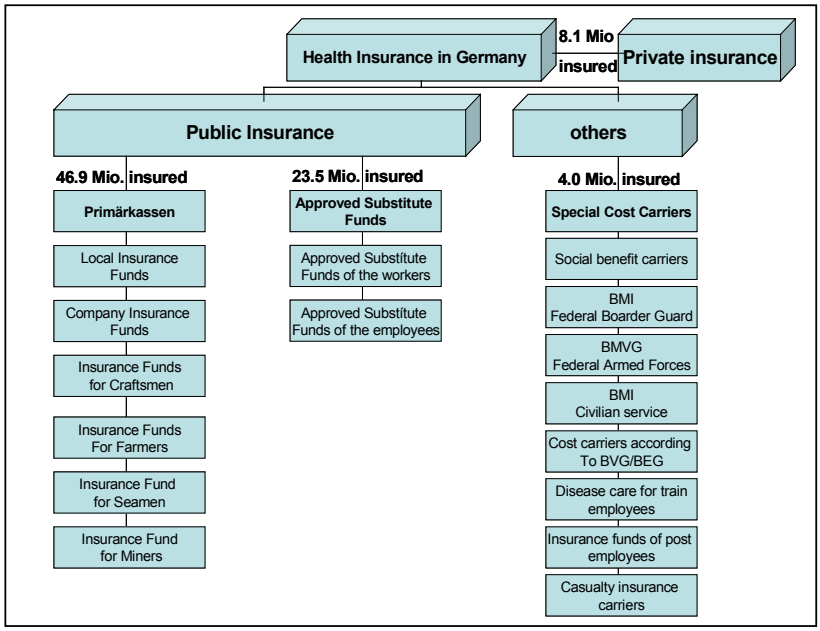
[128] Busse, R. (1999) 'Priority-Setting and Rationaling in German Health Care Systems', *Health Policy*, Vol. 50, pp. 71-90.

suppliers and insurances as financing institutions. The German health system is based on a social model, the so-called Bismarck-Modell. There are five corner pillars of the German social insurance system: the pension insurance scheme, the health and nursing care insurance, the unemployment insurance and the accident insurance.Because of this division, the reimbursement system is also highly fragmented. The greatest part of medical care provided by general practitioners and in hospitals is covered by the health insurance payments.

In the following outlines, the health insurances are predominantly discussed as they contribute to the major part of the system. Yet, the insurance situation is double tracked. Two alternative (or supplementary) systems co-exist: the public and the private insurance systems. These two systems vary enormously in their organisation, calculation of contributions and charging of services. In 2003, 82.5 million people were insured of which 74.4 million (90.2%) belonged to the public insurance scheme and only 8.1 million (9.8%) were in private insurance programmes (Figure 5.2).

The cost carriers in detail can be viewed in the following table. The public health insurance sector carries the greatest part of the costs of 133,348 million euros (around 57 %).

Figure 5.2 Overview of private and public insurance situation



Source: Kassenaerztliche Bundesvereinigung (2005)[129]

Nearly everyone residing in Germany is guaranteed access to high-quality comprehensive health care. Statutory health insurance (Gesetzliche Krankenversicherung-GKV) has for a long-time provided an organisational framework for the delivery of public health care. It has shaped the roles of payers, insurance or sickness funds, and providers, physicians, and hospitals since the Health Insurance Act

[129] Available at http://daris.kbv.de/daris.asp

from 1883.

Statutory health insurance in Germany through sickness funds is compulsory for workers and employees whose gross income does not exceed € 3,375, for unemployed and retired people, and for certain other population groups (such as farmers, artists, and students). Employees with incomes above this threshold may be voluntary sickness fund members if they have been members before.

The services provided are funded through regular contributions by its members. Employers and employees each pay half of a member's premiums. Premiums are set according to earnings rather than risk and are not affected by a member's marital status, family size, or health; they are the same for all members of a particular fund with the same earnings.

Basic principles of the system are the principle of solidarity that grants equal access to all its members independent of income and individual risk and the principle of benefits in kind that ensures free delivery of medical services. More and more a third principle is being established: the principle of subsidiarity that manifests itself in a growing number of supplementary contributions by the insured (e.g. within the latest regulation, the so-called 'Gesundheitsmodernisierungsgesetz', some services were excluded and a compulsory fee for physician visits of 10 € were introduced).

The system consists of a variety of statutory health insurance providers that are subject to public law but that are self-administered and financially independent from the government. Yet they are supervised by the 'Laender' and the federal government. There exist eight main types of statutory health insurance providers (for historical reasons).

Since the beginning of 1996 – with a few exceptions – all insured people in Germany have the freedom of choice among these insurance funds. In particular the local insurance funds and the approved substitute funds are obliged to contract. The introduction of free choice among sickness funds in Germany was accompanied by a risk structure compensation (RSC) mechanism with the aim to balance varying contributions because of heterogeneities in the structure of the clients. Because chronically ill people were not adequately taken into account, competition for newly insured consumers concentrated on the healthy. The introduction in 2002 of disease management programs addresses this problem. Insured people in such programs are treated as a separate RSC category, making them a more 'attractive' group that no longer generates a deficit.

To grant an adequate treatment at any time, the sickness funds enter contracts with health providers. This does not happen separately for each sickness fund but on an aggregate level through Landes – or federal organisations, as already described.

The different insurance funds are all represented through their own federal syndicate. Within their contracts they shape most of the in- and out-patient payments. To grant equal standards of treatment in the statutory health insurance system in spite of this fragmentation of providers, the respective 'Bundesverbaende' again are assembled in the 'Spitzenverband der Krankenkasse'. These are committed as contractual partners of

the health care providers.

According to the Fifth Book of the German Code of Social Law (SGB V), sickness funds have to pay for all new pharmaceuticals that comply with the general current state of medical knowledge, and that are adequate, appropriate and economical. They may not exceed an essential level.

This leads to the fact that apart from a few exceptions (Negativliste) that are listed and regulated separately, all new pharmaceuticals are also repaid. The only means to control costs is by publishing guide lines that have the character of mere recommendations, by alleging global budgets or benchmarks and since the reform act of 1989 by giving price limits, so-called Festbetraege (fixed amounts of money for a specific group of pharmaceuticals).

Another attempt to cut costs was the trial to establish a 'Positivliste', a list including all pharmaceuticals that will be paid by sickness funds (contrarily to the Negativliste). It failed at the end of 2003 within consensus negotiations between the government and the opposing parties. The latest health bill in Germany is called 'Gesetz zur Modernisierung der Gesetzlichen Krankenversicherung' (GKV) introducing additional contributions by patients, an additional fee when going to the doctor's, a freedom of the patients to choose to pay in advance and get the money back from the sickness fund ex post, etc.
Regarding the reimbursement of services within the clinical sector between sickness funds and physicians, the system has also undergone fundamental changes that are noteworthy.

The imminent problem of a changing age structure in all populations of developed countries requires changes in the respective financing model. Germany has approached this problem via the introduction of a case-based lump sum model known as Diagnosis Related Groups (DRG) for the payment of in-patient clinical treatment. The allocation of funds to one of these groups is carried out on the basis of different parameters, among them: main diagnosis and occurrence of complications. Laboratory services are as well included in the respective diagnose related groups and not seperately reimbursed. For a non-clinical setting, the 'Einheitlicher Bewertungsmaßstab' (EBM, standardised evaluation scale) is the relevant body of rules. This code as well has undergone changes and is since the beginning of the year 2005 compulsory in its current version called 'EBM 2000 PLUS'.

The overall expectation and perception of molecular medicine can be characterised as sceptical. However this results mainly from a general scepticism and diffuse fear of ethically problematic fields such as genetic testing in general. PGx itself is not a subject of a general debate. People and organisations that had been exposed to PGx related questions vary strongly in their expectations. Patients tend to have high expectations in individualised therapy especially in the case of cancer therapy. Others e.g. sickness funds and regulatory authorities assume that PGx will have earliest a mid term perspective until it will affect the German health care system. Common answers to the questions were 'call again in two to three years, then we may be able to comment on your questions'. Representatives of the health insurance sector are in an ambivalent position regarding PGx applications. Chances are a more effective use of resources with less money spent for side effects and probably shorter hospital stay cycles. Risks are a

higher financial burden due to higher prices for innovative pharmaceuticals for smaller targeted markets, supplementary costs for diagnostic tests and with more people surviving or turning into chronically ill patients.

5.2 Regulatory framework for medicinal products

5.2.1 Governance structure

In Germany, due to the country's characteristic federal structure, governance is parted between the federal government and the Laender. It is up to both institutions to set the framework of the social health system. The federal government obtains the legislative competence to set the frameworks for the statutory health insurances, including for example the compulsory coverage and the policyholder‘s entitlement to insurers‘ performances. The Laender are indirectly involved in this process through the so-called 'Bundesrat', the German Federal Assembly. They exert administrative competencies.

The Ministry for Health (Bundesministerium für Gesundheit und Soziale Sicherung (BMGS)) is the key institution at the federal level. It concentrates on the development of drafts for new legislations and administration instructions.

The following further institutions in the German healthcare system are directly responsible to the BMGS. They represent the framework for the German health system and the approval procedure.

5.2.1.1 Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

BfArM is the Federal Insitute for medicinal products and medical devices. This institution is responsible for the approval of pharmaceuticals in Germany. Basic principles are effectiveness, harmlessness and adequate pharmaceutical quality. To control the risks of a pharmaceutical after approval and wide application on the market, it collects and evaluates reports of adverse events provided by physicians. Supplementary, it is responsible for the registration, evaluation and assessment of risks adherent to the use of medical devices and to coordinate adequate measurements. (In the case of in vitro diagnostics vide Paul-Ehrlich-Institut below.)

5.2.1.2 Paul-Ehrlich-Institut (PEI)

The approval competence is in some cases shared between the BfArM and the PEI.
The following fields of activites underly the competencies of this institute:

- approval and testing of (immuno)biological pharmaceuticals, mainly serums and vaccines;
- monitoring of the safety of the concerned pharmaceuticals;
- discovery and development in the field of the concerned pharmaceuticals, specifically in the field of investigation procedures;

- determination of standard values for the concerned pharmaceuticals as well as development of standard compounds;
- support of the responsible regional authorities in line of the application of authorisation for the production of the concerned pharmaceuticals;
- support of the responsible regional authorities in supervising the commerce of the concerned products.

5.2.1.3 PEI-IVD

Since the 07.12.2003, the validation of in vitro medical devices has to be conducted according to the European IVDD (Directive 98/79/EG). To comply with these standards, the PEI has established a testing laboratory, called PEI-IVD. Already since the year 2000, this reference laboratory is accredited according to the DIN EN 17025 and Directive 98/79/EG to guarantee high-quality testing of medical devices.

5.2.1.4 Robert-Koch-Institut (RKI)

The RKI is the central institution of the federal government in the field of supervision and prevention of disease. Its core competencies include the detection, prevention and abatement of diseases, especially infectious diseases. Prior tasks are the academic, epidemiological and medicinal analysis and evaluation of diseases characterised by a high danger, high rate of diffusion and high public and health political meaning.

5.2.1.5 Deutsches Institut für medizinische Dokumentation und Information (DIMDI)

DIMDI is the German institute for medical documentation and information. This institute is mainly responsible for three tasks:

- provision of information on medical issues
- development and provision of database-driven information systems for pharmaceuticals and medical devices
- establishment of a documentation and a database-driven information systems for health economic assessment of medical procedures and technologies

5.2.1.6 Institut für Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)

This is the Institute for quality and economic efficiency in the public health system). This institute was founded in the course of the health care reform in 2003. The aim was to establish an independent body to scientifically evaluate the medical benefit, quality and economy of medical services. This includes an assessment of medical treatment guidelines, the formulation of recommendations, the benefit assessment of pharmaceuticals as well as the editing of information to patients. Their scope of duties includes pharmaceuticals as well as medical devices. As it is still in its infancy, no

evaluations on pharmacogenetic issues are assessed up to now.

5.2.2 Principal regulatory situation

Germany is characterised by a dual system for the approval of drugs and medicinal products. In general approval of drugs is carried out by the Federal Institute for Drugs and Medical Devices (BfArM). For certain drugs in the field of (immune)-biological drugs such as sera, vaccines, blood preparations, test allergens, test sera, and test antigens the approval procedure was assigned to the PEI.

The regulatory framework is set by the Drug Law (Arzneimittelgetz, AMG) that ensures the safety of drugs which is defined by the terms quality, efficacy and harmlessness.

Medicinal products are – in contrast to other countries such as the US – excluded from the drug approval process. They are subjected to a validation process. The regulatory framework is formalised by the medicinal products law (Medizinproduktegesetz, MPG). The European In-Vitro Diagnostic Guideline (RL 98/79/EG) which regulates the placing on the market was integrated into the medicinal product law in January 2002 in the course of the German second Medizinprodukte-Aenderungsgesetz (changed law governing medical devices). This law regulates the production, distribution and operation of medical devices with the aim to ensure the safety, appropriateness and operating efficiency for the patient as well as for the user.[130] The law ensures that medical devices must be subject to a process of certification, the so-called CE-certification (conformité européenne) in order to grant minimum quality levels.

Criteria are e.g. sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurement range The certification process consists of a validation by newly installed 'notified bodies'. For in vitro diagnostic products an inspection authority was established end of 2003 within the Paul-Ehrlich-Institute as separate unit, called PEI-IVD. This new testing laboratory cooperates with other notified bodies in the field of in vitro diagnostics. The validation of other medical devices is carried out by the BfArM.

5.3 Regulatory framework for PGx products

PGx applications consist of a pharmaceutical/diagnostic test combination. Prerequisite to grant safe applications in this new field is an effective approval process. So far, no pharmacogenetic specific process for approval has been designed. As described above Germany has two different bodies of authority both for the approval of pharmaceuticals (BfArM and PEI) with again separated authorities for the validation of medical devices.

5.3.1 Approval of PGx products

In principle, both authorities can be concerned with PGx applications. Applications of

[130] Anonymous (2005a) available at http://www.aok-bv.de/lexikon/m/index_02300.html.

targeted therapies are mainly anti-bodies that are within the scope of responsibility of the PEI (examples named were trastuzumab (Herceptin®), rituximab (MabThera®), erbitux (Cetuximab). Yet, 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 proceeding is to examine the pharmaceutical on its quality, efficacy and harmlessness as dictates the standard procedure. In case it turns out within clinical studies or is even known beforehand, that only a subgroup of the whole population profits from the medication or that the dosage has to be adjusted according to the individual genotype, basic pre-requisite is the existence of a respective validated method that allows the identification of the relevant subpopulation. An 'academic assessment' within the general assessment of efficacy of the pharmaceutical takes place evaluating existing data from clinical trials on the sensitivity and specifity of the test in question, that is: a reliable method has to exist on the market that can be applied.

Critique was exerted on the current regulation that authorities may not, according to existing law, impose the use of a specific test on the physicians. It was stated that apart from assessing whether there exists a principally appropriate test, the authority's 'hands are tied'. This leads to the problem of remarkable differences in the quality of conducted tests. This is a big disadvantage compared to the US regulation where both, pharmaceutical plus test are approved by the same body of authority.

Further, the problem was formulated that the itemised devices in annex II of the IVD directive were not all-embracing. Specifically, those methods applied for current pharmacogenetic purposes are not included and therefore need not to be validated according to this directive. Here, adjustments should be made according to the interviewed expert.

Regarding the BfArM, a quite similar proceeding became apparent. The authority stated that two complete different issues and separated procedures are concerned. Standard proceeding was thus to approve the pharmaceutical and to refer to an existing validated test. It was emphasised that the respective test needs to be validated beforehand. In unclear cases, feedback with the former responsible validation authority was considered.
Exemplarily, the questioned person referred to other cases of product/test-kits where the responsible authority for the validation of the test was again contacted to clarify the case, such as in the case of one asthma pharmaceutical and affiliated spacer, referring to the regulation in MEDDEV 2.1/3 rev 2 from July 2001, section C. For so –called combination products (medical devices that contain an active ingredient), there exists a special obligatory consultation process between the approval authority and the validating authority. Yet, a similar procedure for PGx products is not envisioned.

Companies that have experience with the approval process described the German situation as good and consistent. Roche itself claimed that everything went smooth during the approval process of Herceptin® and their outlines were in line with the just stated procedure. As there was already a certified 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 process. On the part of the pharmaceutical industry, no critique was reported in this respect. Companies do not

believe that any hurdles will blockade the way to new marketable products. The work of the respective authorities in Germany was consistently generally approved by industry.

Further strictly excluding tests comparable to Herceptin® do not exist at the moment mainly due to the claimed fact that there is rarely a 1:1 correlation between response or development of adverse events and genetic profile of the respective patient. As we are talking about 'mere probabilities' according to one interviewee, companies rather hesitate to deny access to a specific subgroup and rather reduce the average dosage recommendation to a medium compromise as long as possible. This procedure is critical in two respects: First, this might be contrary to the declared aim that pharmaceuticals have to be applied in an economical way and secondly it has to be ensured that physicians consider possible severe outcomes.

5.3.2 PGx and patent protection

At the end of 2004, the German government finally converted the European biopatent directive into German Law. This has for a long time been claimed by representatives of companies and has now been warmly welcomed.

Worth mentioning is the fact that- as stated by the questioned experts in the academic sector (public research institutions) – patents only play a minor role in the field of pharmacogenetics. They currently only serve as a means to show the state as financial donor that a lot of research is being conducted that can potentially be turned into market applications with the aim of not running out of urgently needed funds. There's no direct financial intention behind it. Because of the uncommonness of using pharmacogenetic tests nobody has ever been blamed for not paying patent fees.

5.3.3 Orphan Drug Law

Referring to PGx, many people talk about a market revolution with pharmaceutical companies turning away from blockbusters towards 'mini-busters'[131]. To turn smaller market segments into a possible attractive target market, corresponding incentives for companies to invest here have to be offered.

The VO 141/2000/EG, so-called Verordnung über Arzneimittel für seltene Leiden, dating from the year 1999 and its affiliated executive regulation (VO 847/2000/EG)[132] basically correspond to the American Orphan Drug Law and represent one step to facilitate and boost investments in smaller targeted segments. This status should also apply for 'orphan genetic groups', which is not guaranteed at the moment.

5.3.4 Reimbursement of PGx products

[131] Melzer, D., Raven, A., Detmer, D.E., Ling, T. And Zimmern, R.L. (2003) 'My very own medicine: What must I know?', The Welcome Trust, p. 30.

[132] Ambrosius, M. (2003) Pharmarecht, available at http://www.jura.uni-marburg.de/zivilr/voit/Pharmarecht/dokumente/ss03/section8part1.pdf.

A special feature of the German health care system is the important role in the regulation of medical provision that is played, alongside that of the legislature, by the self-governing body of doctors and health insurance funds. The legislature creates the legal framework; the medical self-governing body, formed from the national associations of doctors and dentists, the German Hospital Federation and the health insurance funds, gives concrete definition to the legal stipulations and implements them.

The paramount decision-making body of the joint self-governing body is the Federal Joint Committee (Gemeinsamer Bundesausschuss (G-BA)). The G-BA has been institutionalised by the legislature as a legal entity under public law. It has wide-ranging regulatory powers. The various duties and wide-ranging powers of this committee are laid down in Volume Five of the Social Legislation Code (Social Code Book No. 5), which governs statutory health insurance.

One important area of responsibility of the G-BA concerns the assessment of new methods of medical examination and treatment. In the sphere of ambulatory care in particular, the G-BA must provide a positive evaluation if a new method, in terms of benefit and efficiency before it can be paid for by the statutory health insurance funds. The Federal Committee's assessment of medical methods and provision follows a standardised procedure which rests on evidence-based medicine. The generally accepted state of medical knowledge is ascertained for the purpose of assessing the effectiveness, quality and economic efficiency of the methods examined.

The G-BA issues the directives that are necessary for safeguarding medical provision. These aim to ensure that provision for those with statutory health insurance in Germany is adequate, appropriate and efficient. The committee issues directives, for example, for such fields as early diagnosis of diseases, dental treatment, psychotherapy and rehabilitation etc.

The G-BA has a central responsibility in the field of medicament provision for those with statutory health insurance. This does not concern the question of licensing medicaments for the German market, which is the task of the Federal Institute for Drugs and Medical Products (BfArM). The G-BA regulates remuneration exclusions and restrictions in medicament provision through directives based on the efficiency requirement.
Thus PGx applications that are judged by the G-BA to be part of the generally accepted medical state of the art and that are cost-effective must be reimbursed. The criteria for reimbursement are: the quality and efficacy have to be conform with the general accepted state of medical knowledge and have to consider medical advances. They have to be sufficient, suitable and economical.

Only the listing in a negative list can exclude them from the reimbursement status. The evaluation of cost-effectiveness is carried out on a qualitative basis. As long as PGx applications comply with these criteria and are not explicitly excluded, they must be reimbursed The recently established institute for quality and economic efficiency in the public health system (Institut für Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)) will add the quantitative analysis for decision making of reimbursement.

5.3.5 Application of PGx products

The framework for genetic counselling and diagnostics is characterised by a huge number of legally non-binding statements. On the part of the federal government, there currently exist no specific statutory regulations for genetic counselling and diagnostics. In current practice relevant authorities are the BfArM and the PEI. However to date there do not exist any initiatives to adopt the framework to the new PGx situation. Aggrevating is the fact that responsibility for drugs and medicinal products is divided between the two authorities.

The most important initiative regarding pharmacogenetic testing is the current draft concerning genetic diagnostic testing **(**GendiagnostikGesetz, GenDG). The draft is an executive bill to article 199 of the German Federal Constitution (BV). Article 199 BV aims at protecting the human and its surroundings regarding possible misuse of the reproduction medicine and gene technology in humans.

It is stated that genetic tests may only be conducted if the concerned person affirms its willingness to participate. The aim is to protect human dignity, to prevent misuse and to safeguard minimum quality levels. Genetic tests for medical purposes have to serve a preventative or therapeutic aim or serve as the basis for individual family or life planning.

It also denies employers and insurance companies access to such data except for certain cases (insurance sum above a threshold of 250,000 € or yearly rent above 30,000 €). Still, one has to consider that it's just a draft version that will probably not come into being the way it is now. According to interviewees, the main principles of the planned law are basically approved of. Yet, there are some issues that will have to be further discussed. One example is the general drafted ban for (private) insurance companies to gain access to genetic data. This regulation corresponds to the current voluntary self commitment of insurance companies that is listed in table 12. Yet, the self commitment is limited to a time horizon of another six years whereas a law would be fix. Arguments against this strict regulation are to be found in the character of private insurance companies per se. These institutions are based on risk assessment to be able to outbalance their patient portfolio. Another counter argument that was forwarded is that of method discrimination between other diagnostic tools and genetic diagnostics.[133] Insurance companies as well as other actors will probably claim their stake on the current version before the law finally comes into being.

Talking to one member of the enquete commission 'Rights and Ethics in Modern Medicine' it was clear that their position is to rather rule out all possible critical points than having a situation later on where misuse can happen. Consensus was reached on the fact that not the method is determining, but the outcome, notably whether the results are of predictive or diagnostic value which has been considered within the law.
The chances and risks linked to the use of genetic diagnostic methods in humans are extensively discussed by special commissions and tasks forces founded by the federal or Laender governments. These are not of legally binding character. Among these are the

[133] Taupitz, J. (2001) 'Legal aspects of genetic tests in health insurance', available at www.paul-martini=stiftung.de/de/veranstaltungen/2001_workshop_abstract.pdf

so-called Benda commission from 1985, a common task force between the former Federal Ministry for Health and Technology and the Ministry for Judicial Affairs, dealing with controversial issues such as in vitro fertilisation, the analysis of the human genome and gene therapy.

Further reports were written in 1987 by the enquete commission 'chances and risks of gene technology', in 1990 by a regional (Laender) task force called 'genome analysis' and in 2000 a position paper by the ethics advisory board of the Federal Ministry for Health forwarding ethical and legal issues in the handling of predictive genetic tests.
In 2002, the then Enquete Commission, Rights and Ethics in Modern Medicine, published an all-embracing final report (14/9020), including the following sections:

- general ethical and legal issues, such as Human Dignity and Human Rights and further individual and social issues,
- an outline of pre-implantation diagnostics as main part,
- an assessment of the state of the art and possible regulation proposals concerning genetic data in general.

In this report, pharmacogenetic as a growing field is included in the category 'individual genetic tests for diagnostic and predictive purposes'. Its potential benefits and current state of the art are outlined. It also takes a critical glance as it fears growing prices of medication because of smaller targeted patient groups. According to them, the health systems will be confronted with the problem of how an equitable allocation of rare resources can be achieved in the future. It addresses different issues that have to be regulated, such as

- a right to know and not to know
- Consent
- protection against discrimination
- data protection

Many of these issues and proposals have been considered in the current draft of the 'Gendiagnostikgesetz'.

In addition, there exists a number of different position papers by German organisations, but none of them has a legally binding character. Some of these position papers are listed briefly in Table 5.1 below (that do not necessarily include pharmacogenetics but rather genetic methods in general).

Table 5.1 Different Statements on Genetic Issues

institution	Statement	year
German Society of Human Genetics	position paper on genetic diagnostic in children and adolescence	2000
	declaration on life insurance and genetics	1999
	position paper: DNA-sampling and personal data in biomedical research: technical, social and ethical issues	2004
	position paper: genetic diagnosis for disposition factors on diseases and development disturbances as well as drug reaction due to multiple factors	2004
Board of Medical Genetics	information regarding genetic counselling and informed consent	1994
	position paper and recommendations regarding problems linked to professional discretion	1995
	proposal on information regarding medical genetic laboratory tests and informed consent	1995
	further education in ethical and psychological basics of genetic counselling	1996
Board of Medical Genetics, German Society of Human Genetics	Guidelines for genetic counselling	1996
	Guidelines for molecular genetic laboratory diagnostic	1996
German Medical Association	Guidelines on predictive genetic testing for tumour disposition	1998
	Guidelines on predictive genetic testing	2003
German Insurance Association	Voluntary formal commitment of member companies (self commitment) not to take any existing predictive genetic data into account in their risk assessment nor to order any predictive genetic testing, only exception: insurance sums above a total of € 250,000, or yearly rent above a threshold of € 30,000, respectively limited until at least 2011	
Association of German researching pharmaceutical companies (Verband Forschender Arzneimittelhersteller e.V., VFA)	Position paper/self commitment to stick to basic ethical and legal principles including the protection of data	2004

5.4 Regulation of clinical testing services

As discussed in the previous chapter, there are no common statutory regulation specifically for pharmacogenetics. However the general accreditation procedure applies also for PGx related activities.

5.4.1 Laboratory accreditation

To safeguard quality, three management techniques are available: accreditation,

certification and Good Laboratory Practice (GLP). In 1990, the term GLP was legally introduced in line with the German Chemicals Law. In this law, basic requirements to protect the public, especially the health and security of users and the environment are formulated. For each chemical entity a separate risk assessment is laid down.[134]

Responsible for accreditation in Germany are the following organisations: German Accreditation Organisation (DACH (Deutsche Akkreditierungsstelle), German Accrediation System Testing Body (Deutsches Akkreditierungssystem Prüfwesen GmbH (DAP), Central Authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices (Zentralstelle der Laender fuer Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG)). The application for accreditation has to be filed at the accreditation organisation. The accreditation includes the formal approval of the competence of an institution including quality of structure (qualification of personal, infrastructure, documentation), quality of procedures (methodology, communication strategies, collaboration), and quality of results (diagnostic of disease, patient contentment). Basis for accreditation is ISO 15 189 ('Medicinal laboratories – specific demand for quality and competence'). The successful accreditation is attested by a certificate of the German Council for Accreditation (Deutscher Akkreditierungsrat (DAR)).

For the last ten years, some advocates of compulsory quality management have already claimed a certification for medical institutions. Common certification methods like EN ISO 9001:2000 and accreditation methods like EFQM® that are widely spread within other industrial sectors have been adopted for medical institutions as well. In 1996, important actors of the health care system supported by politics have come together to develop a certification method adjusted to health care needs. With the introduction of KTQ® (cooperation for transparency and quality in hospitals) and proCumCert (a confessional certification association with the aim to safeguard and promote further advancements in catholic hospitals and other social institutions) in the year 2002, an all-embracing certification method is now available for hospitals. The method relies on basic principles and criteria set by DIN EN ISO and the European Foundation for Quality Management (EFQM).

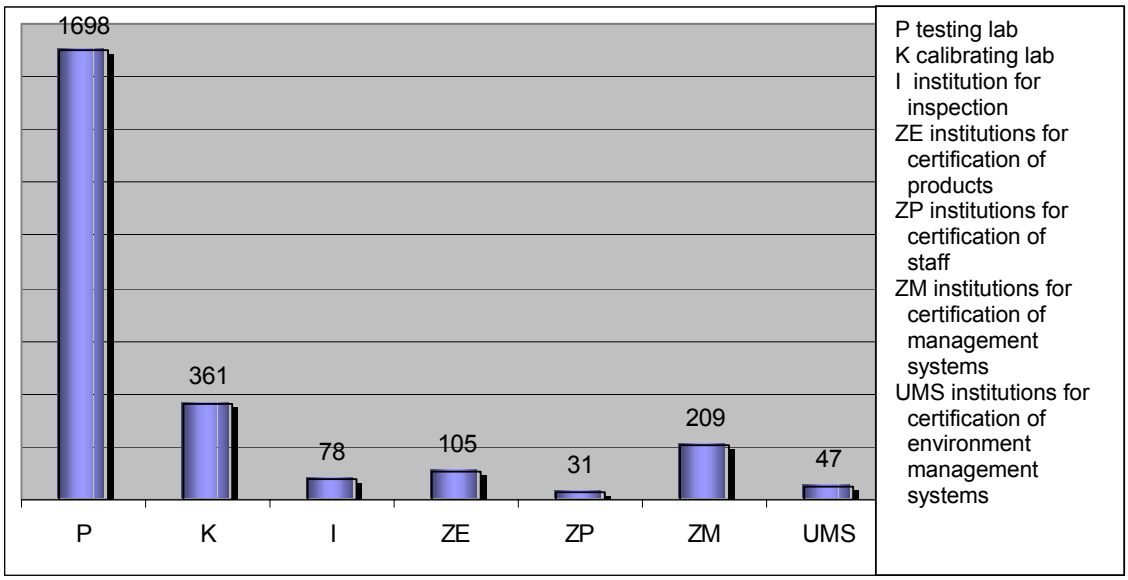
Regarding actual practice, it must be stated that it's currently not compulsory for laboratories to be certified for example according to DIN/ISO 9000 et sqq.

Within the interviews, it was noticed that most laboratories in hospitals are not certified according to ISO standards and do not approve of the implementation of these systems as this was said to be accompanied by additional bureaucratic workload and costs.

Regarding independent external laboratories, certification and accreditation are more common means simply as quality indicators as they are exposed to market competition. According to the German Council for Accreditation, on the whole 1,698 testing laboratories were accredited in the year 2005 (figure 3). This figure does include medical laboratories that conduct PGx test, but not uniquely.

[134] Schüttpelz, K. (2003) 'Auswirkungen der Akkreditierung von Pruflaboratorien und Zertifizierungsstellen von Produkten in Deutschland, available at http://edocs.tu-berlin.de/diss/2003.schuettpelz_katrin.pdf

Figure 5.3 Number of laboratories accredited in 2005



Source: German Council for Accreditation (Deutscher Akkreditierungsrat)

Another relevant institution saw the general trend as throughout positive: The number of laboratories filing new applications was increasing throughout 2004. According to this source, most of these laboratories were medical diagnostic ones.[135]

5.4.2 Quality assurance

In 2001, the European in vitro-diagnostic directive was converted into national law within the amendment (revised form) of the German Medizinprodukte-Gesetz (MPG, bill on medical devices). According to §6 MPG, medical devices may only be placed on the market and put into operation if marked with the CE-certification.

It is therefore compulsory for companies to certify their products before introducing them on the market to safeguard patients, as well as users and third parties. (MPG § 1) This regulation ensures a minimum standard of the devices used in laboratories. Every company introducing a non validated test would incur a penalty.

Affiliated to this regulation was the so-called 'Medizinprodukte-Betreiberver-ordnung' (MPBetreibV, 2002) that regulates the setting up, operation and use of medical devices. Providers of diagnostic testing services have to assess the quality of their offered services regularly. Paragraph 4a states that results of measurements have to be guaranteed via regular check-ups (internal quality assurance) and via participation at comparison studies per quarter (interlaboratory tests/ ring studies- external quality assessment).

Parallel to this attempt to regulate the quality of medical devices and linked services,

[135] Deutsche Akkreditierungsstelle Chemie GmbH (2004), available at http://www.dach-gmbh.de/download/news/NACHR18.pdf

the German Federal Medical Association has released a guideline on the quality assurance of quantitative laboratory analysis that has come into being with the year 2003. Attached to this regulation, there's a list of included norms and allowed deviations from given benchmark values.

In the case of contractual services, this certification also serves as prerequisite for the reimbursement decision for quantitative laboratory services. Therefore a financial indirect coersion to participate exists as well. Within the standard charging list (EBM), it is noted that these services are only billable, if quality requests by the German Medical Association are being fulfilled.[136]

With the renewal of the German Code of Social Law (SGB V1) in the course of the modernisation act of German sickness funds (GKV-Modernisierungsgesetz) in 2004, the legislator explicitly formulates the requirement for doctors to ensure and promote the quality of their services. § 135 II SGB V represents the basis regulation for quality assurance within all contractual medical services. The new § 135a SGB commits contractory physicians, medical supply centres, as well as hospitals to

- participate at external measures of quality assurance and to
- introduce internal quality management systems.

All approved hospitals therefore have to establish an internal quality management system as well as external measures. From the year 2005, hospitals that do not introduce a quality management system will suffer from financial compensation losses. Yet, this formulation does not specify what measures exactly to take. According to the succeeding paragraph (§ 136 a,b), it is up to the Common Federal Committee of physicians and insurance funds (Gemeinsamer Bundesausschuß, G-BA) to define precise standards for an adequate internal quality management system.

On the basis of this regulation, several agreements have been introduced. Yet, talking to pathologists, this regulation was seen as too broad to bear direct consequences for laboratory practice. Still it was stated that clinical laboratories will potentially come more and more into pressure to participate at external as well as internal quality assurance schemes.

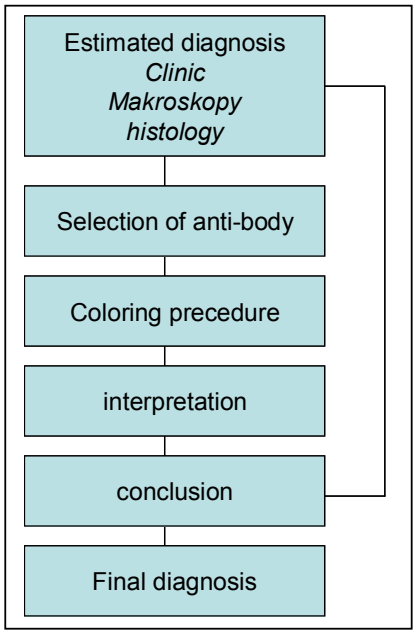
Regarding the field of immunohistochemistry, no common, legally binding quality assurance scheme exists, according to interviewees. Pathology as a specialty relies on pattern recognition expertise of individual pathologists, a skill that may be subjective. Due to some of the inherent characteristics of IHC, quality control is difficult to formalise. Ring studies are the most important means to guarantee an external quality assurance. In case of a successful participation, the respective laboratory receives a certificate. Within immunohistochemistry, ring studies are regularly being conducted-also at a European Level (Rhodes)-, but they are still on a voluntary basis. The problem has to be seen in the context of the German regulatory system that, contrarily to the U.S. situation, the use of official test kits, such as the HercepTest® or automated CB11 test

[136] Kassenaerztlichen Vereinigung Niedersachsen (2003) 'Qualitaetsbericht 2003 der Kassenaerztlichen Vereinigung Niedersachsen,
available at http://www.kvn.de/kvn/content/internet/kvs/hauptgeschaeftsstelle/011/01/qualiBer2003.pdf

(Pathway™ HER-2 by Ventana)[137] that are certificated, are recommended, but not mandatory. Laboratories approve of this solution, as the official test kits were claimed as being too expensive.[138] Yet, this leads to the widely discussed problem of so-called 'home-brews'.

Interviewees reported that some laboratories or pathological institutes that use the test for internal purposes only order for example parts of the official recommended kits and tailor the rest, especially the colouring anti-bodies, by themselves ('home-brews'). The reported reason for this proceeding was a lack of financial means as these tests were reported to be rather expensive. These home-brews are not certified at the moment and this might represent a source for wrong diagnostic findings as it can be assumed that not all of the laboratories dispose of the adequate expertise to generate for example the staining antibodies by themselves. Feedback from DAKOCytomation itself revealed that probably only around 20 to 25 % of all anti-bodies are procured from them, despite being the biggest supplier.

Figure 4 Single steps of clinical immunohistochemistry



Source: Rüdiger et al. (2003)[139]

The whole process of immunohistochemistry was said to consist of a high complexity

[137] Bilous M, Dowsett M, Hanna W, Isola j, Lebeau A, Moreno A, Penault-Llorca F, Ruschoff J, Tomasic G, Van de Vijvier M. (2002) 'Current Perspective on HER-2 Testing: A Review of National Testing Guidelines', *Mod. Pathol.* Vol. 16, No. 2, p. 176.

[138] U.S. laboratories were said to be better financially supported to be able to carry the costs of approved test kits.

[139] Rűdiger, T., Hőfler, H. Kreipe, H. Nizze, H., Pfeifer, U. Stein, H. Dallenbach, F. Fischer, H. Mengel, M. von Wasielewski, R. and Mller-Hermelink (2003) 'Ringversuch 2000 'Immunhistochemie' der Deutschen Gesellschaft fur Pathologie und des Berufsverbandes der Deutschen Pathologen', *Der Pathologe*, Vol. 24, pp. 70-78.

that was hard to evaluate externally. Within one big German ring study conducted in the year 2000, several different critical steps have been identified that would need to be considered in a quality assurance scheme (figure 4). The most critical parts were identified as choosing the appropriate antibodies and an adequate interpretation of the results. Still, most current studies focus on smaller parts of the process, specifically the colouring process.

Regarding the field of process quality, an often mentioned critique was that the familiar paths or proceedings of interaction between physicians and laboratory doctors should be reconsidered. As laboratory doctors are generally more specialised on new currents and the latest knowledge of phenotype-genotype interaction one might discuss whether they should further be integrated into the decision making process to offer the patient the best possible treatment and to profit from arising synergies.

5.4.3 Staff training and best practice

Since 1st January 2004, contractual physicians, authorised physicians and hospital physicians in Germany are obliged to participate at further education programmes. This regulation has been introduced in the course of the German law to modernise statutory health insurance (GKV-Modernisierungsgesetz, GMG). In case of refusal to do so, the physician has to expect punishments ranging from economical losses to a complete withdrawal of his or her authorisation to practise. This regulation is to be found in § 95d GMG. Whether this is an effective means can be put into questions as it is still up to the physician to choose which courses to attend.

During the interviews it was realised that- in case the theme was common at all- it was the laboratory physicians who disposed of the latest knowledge in this field. The attending physician was often ignoring these correlations. Still, it is him who is at the front-line and who has to commission the test in question. This represents a gap that is hard to overcome.

Concerning linked quality topics, it was said that the best guarantor for quality within a laboratory was the fact that the pre-requisite to be allowed to practise as a laboratory physician is the specialist title which results from an additional professional training on the job after the basic medicinal curriculum at the university.

Yet, the laboratory team is often composed of different disciplines such as chemists, biologists, etc. that are not obliged to take part at further education programmes. To guarantee the accuracy of the reports, it is therefore compulsory that a specialist physician monitors his colleagues and sets his signature under every report.

5.4.4 PGx in clinical trials

According to one company representative, ‘lots of genetic data are being collected in clinical trials’. As realised in the interviews, PGx is of great importance in all of the following areas:

- target discovery

- target optimisation in preclinical setting
- compound optimisation in preclinical setting
- patient stratification in clinical trials and retrospective data evaluation.

A clear guidance for the elevation, procurement and storage of genetic data as well as probes is according to interviewee information still missing.

Key guideline is the regulation on Good Clinical Practice during the performance of clinical trials with pharmaceuticals for human use that came into being in August 2004. Within this regulation, European Law that aimed at assimilating different national guidelines was converted into national law. According to these European requirements, clinical trials may not be conducted without a positive vote on the part of the respective ethics committee and the responsible federal authority. The aim of this procedure is to warrant a broad assessment of the project including academic and ethical issues.

These ethics committees are the guarantors of basic rights within trials also including the elevation of PGx data. They are reported to be the greatest hurdle on the way to a marketable product in the field of PGx be it on a national or on a European level in case of multicenter studies.

The work of these ethics committees is not subject to standardised procedures and a common legal basis. They have their origin in different rights on different levels and are characterised by plurality due to the German federal structure. Every single one has established own norms and standard procedures which leads to the fact that some are stricter in the number and quality of required documents and procedures than others. A few of them have developed own standard requirements regarding genetic data including adequate information, written consent, a strict disjuncture of the genetic part of the clinical trial and all other parts (to allow general access to patients independent of their willingness to participate at genetic tests), anonymisation of medical data, etc..

Given this heterogenic structure and unequal proceedings they've often been critically discussed. In the view of that, the German Ethics Committee for Rights and Ethics in Modern Medicine has commissioned a report in 2004 on the actual structure of ethics committees in Germany including a variety of improvement proposals. This report has not been further evaluated yet by the commission.

Some of these issues, such as an 'opt-out option' for patients regarding genetic aspects within clinical studies are already implemented within interviewed pharmaceutical companies. It was reported that different informed consents exist. But not only the national configuration is of importance, but also the European situation as most of the studies including the elevation of pharmacogenetic data are multicentre studies.

In the view of turning Europe into an attractive site for pharmaceutical studies this is an urgent theme. Representatives of companies complain the diversity of different local requirements with which they are confronted before actually being able to conduct a study. This is consuming many resources (time, efforts and money) on the part of the companies and makes Germany and Europe as a whole less attractive as region.
Within the current draft of the German GenDG, attempts have been made to rule out problematic themes within research programmes, such as informed consent, education

and anonymisation of probes. However, this is not yet agreed upon. Still, companies claim that the actual draft is research benign and rather supports studies.

Talking to representatives of the pharmaceutical sector, the impression was gained that they are rather satisfied with the current situation as they fear that an adjustment of rules on a European level would rather tend to be more conservative. A medium compromise would be hard to achieve.

Comparing the European situation to other markets, the surprising fact was gained that the prevailing situation in Europe was not reported to differ much form other countries, referring to clinical demands. The lately released 'Voluntary Genomic Data Submission Guideline' by the FDA would in great parts set out in writing what has been practised for the last couple of years within standard clinical protocols. German clinical researchers both at companies favour EMEA to follow the FDA guidelines on a European level rather than having national legislation.

5.4.5 Lab-customer interface

As widely criticised by the laboratory medical profession, the lab-surgery interface leaves a few issues to be desired.

Attending physicians often claim that the reports they receive back are incomplete, fragmentary and do not give a clear instruction as a guideline for further treatment. It was noticed during the interviews that this was partially a problem linked to the contacted lab. Whereas clinical pharmacologists are further involved in the clinic and individualise the tests and the respective report, external labs that offer these services as they are equally well technically equipped approach the theme differently and often proceed shorter, less distinct reports.

On the other hand, laboratory physicians claim that they are not sufficiently involved in the clinic of the individual patient. Many more synergies could be realised and better diagnosis could be achieved if the relationship between the two disciplines was closer. Especially with the interrelations getting more and more complex, improvements are desirable. Whereas pathologists seem to struggle in this field, other concerned disciplines seem not yet as sensitised.

Regarding quality aspects, labs claim that their own influence on the whole process is not sufficient as they do not have a say for example on how long probes are stored before arriving in the lab.
Regarding PGx, more and more phenotype-genotype correlations are being detected as seen in the case of TPMT with 17 current relevant SNPs discovered. Among these, only a small sample is being tested. Which ones exactly to choose should not only be within the scope of duties of the attending physician, but also of the laboratory expert.

To make use of this knowledge, existing structures and co-operations have to be intensified. It was generally noticed, that laboratory physicians are the driving force and dispose of the furthest knowledge.

This brief outline shows that the communication and cooperation structures can generally be uphold, but should as well be intensified and adjusted to new needs. Experts already now noticed a greater interconnectedness of disciplines.

5.4.6 End-user practice

The success of PGx and the scope of adherent risks is in a great part depended on the actual practice of the end-users.

Different bodies of authorities have published guidelines on the use of product-test kits. Best example in this respect is Herceptin and the adjuvant HER-2/neu test.

Officially recommended are the validated test-kits by DAKOCytomation, so-called HercepTest and Ventana, using CB11 antibodies. As discovered and widely criticised as well by official authorities, these tests are not uniquely applied. Many users apply their own home-brews which is a source of mis-diagnosis as was described in the preceding chapters.

Despite further existing examples where the benefit of conducting a pharmacogenetic test ex ante is known and its application is also recommended, the only widely spread test is still the HER-2 test. This can be explained by the fact that access to the antibody trastuzumab would be denied otherwise whereas in all other cases their use can be avoided. Several reasons have been identified within the interviews that explain this phenomenon and the physicians' hesitation.

They are stated in brief below:

- lack of knowledge among physicians in respect to genetic knowledge as well as statistics suggesting their average age of 50.2 years[140] (relevant because the problem was reported to diminish with newer generations of young physicians).
- lack of existing quantitative data to guide physicians (such as 90 % less dosage for slow metabolisers)
- stimulus saturation due to a huge mass of information and new developments flooding the physicians
- lack of flexibility pared with a belief in methods that have proven to be effective
- mistrust in pharmacogenetic results due to multi factorial nature of interrelations
- hype of the theme too early on when no valid results were presentable
- realisation that pharmacogenetic test represents in some cases no substitute for former methods but a supplementary means, as proven in the TPMT case
- unclear reimbursement situation in the view of physicians.

As was just mentioned, pharmacogenetic insights did in most cases not lead to a restriction in the indication. As long as this is common proceeding, the knowledge will be hard to spread among doctors and side effects can still occur, despite the knowledge.

[140] Aerztekammer (2005), available at www.aerztekammer-bw.de/o5_old/archive/arztzahl.html

Yet, it was noticed that physicians become more and more aware of the problem, but that it always takes a while until new knowledge diffuses among the people.

5.5 Remaining challenges for the regulation of pharmacogenetics

With the first target-specific products on the market, a first step has been taken in the development of PGx. The second followed track to adjust dosing according to individual needs is more in its infants. Regarding long established products, such as Imurek, the incentive is small as well for pharmaceutical companies as for doctors who are quite often stuck in their habits.

5.5.1 Regulation

Up to now authorities did not take any actions to develop new standards for the handling of PGx matters. The trend was to wait until the authority is confronted with the problem. Most likely traditional heuristics for problem solving will be applied and a step wise adoption of existing regulations will follow.

The current attempt to launch a law on genetic testing is the furthest step in this direction. The general starting point is the gained result, not the diagnostic method itself. All great risks are tried to minimise and in its broadest basis it is also approved by everyone.

A major obstacle in the present regulatory framework is the division between the two authorities BfArM and PEI. Interdisciplinary issues and questions relating from the combination of a drug and a medicinal product can not be handled efficiently. Basic knowledge is lost due to deficiency in knowledge transfer. In order to establish an efficient knowledge transfer new structures have to be developed tackling with PGx matters.

5.5.2 Consent and ethical issues

Regarding potential ethical problems, opinions diverge. Companies rather play down the issue and compare the test with other means of generating a diagnosis. Often listed comparisons were that of blood type test and colour blindness (ablepsia). Wide consensus reigned that not the way data is raised is relevant, but rather the derived information itself: the simplest genetic test was said to be rather easy: that of determining the gender of the person vis-à-vis. Whether this is a source for discrimination can be put into question.

5.5.3 Education

To encourage the use of PGx testing there is a need to educate doctors, pharmacists, and nurses. Most people working in the medical sector were not taught the relevant basic knowledge during their training. Additionally expert systems that are easy to handle will further help to introduce PGx testing. However, this requires a broader knowledge base and the improved clinical evidence of the genetic basis of disease. This must be subject of further research on a gene by gene and drug by drug basis.

5.5.4 Quality of testing

Though there is a positive trend to participate at quality assuring measures still a huge number of clinical laboratories are not accredited. Laboratories fear the bureaucratic and financial hurdles and the expenditure of time. In order to further simulate quality assurance a (compulsory) system with transparent and standardised requirements should be developed.

5.6 Primary sources

- 2 Officials from the Medicines and Healthcare products Regulatory Agency (PEI, BfArM)
- 6 Research Laboratories ((Dr. Margarete Fischer-Bosch-Institute for clinical pharmacology, Stuttgart; Institute of Pharmacology, Kiel, Institute of Clinical Chemistry and Laboratory Medicine, University Regensburg, Department of Clinical Chemistry, University Göttingen, Department of Pathology, University of Würzburg, Pathological Institute, University Clinic Kassel)
- 4 Clinical Laboratories (Laboratory for Medical Genetics, München; Centre for Laboratory Medicine, Microbiology and Human Genetics, Mönchengladbach, Department for Medical Genetics and Genetic Advice, University Würzburg, Breast Centre Heidelberg)
- 3 Officials of Sickness Funds (Münchner Rück; Hamburg Münchner Krankenkasse, DKV Köln)
- 3 Company representatives (Hoffmann-La Roche AG, GlaxomithKline, Verband der forschenden Arzneimittelhersteller (= German Association of Research Based Pharmaceutical Companies)
- 1 Official of the German Parliament
- 1 Official of an ethic commission
- 1 Official of the Central Authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices

Chapter 6 Regulatory frameworks for PGx in Ireland

Tony Forde and Jim Ryan, CIRCA Group, Dublin

6.1 Introduction

The Irish Health System is currently in the process of a major reform. The structure had remained unchanged since the creation of regional Health Boards in 1970. The description in this section of past practices should therefore be seen in the light of a system that is currently being dramatically changed. The policy basis of the reform was initiated by the launch of the report '*National Health Strategy'*[141] The strategy set out key objectives for the health system for the succeeding 7-10 years:

- Better Health for Everyone
- Fair Access
- Appropriate Care in the Appropriate Setting
- High Performance.

The reform programme has been developed through a series of reports[142] on the current health system and future needs. It emerged principally from the recommendations contained in two reports:

- The Audit of Structures and Functions in the Health System
- The Report of the Commission on Financial Management and Control Systems in the Health Service.

In June 2003, the government announced the Health Service Reform Programme, which is undertaking the planned changes. The programme has a website[143] which provides full details of all elements of the new system, and the stages in its delivery.

6.1.1 Major health organisations

The three principal bodies in the reformed Irish healthcare environment are:

6.1.1.1 Department of Health and Children[144]

Within the new structure there is a clear separation of the executive and non-executive functions of the Department. The Department will have a dual role in the new structure, which includes focusing on strategic and policy issues (and therefore reducing its involvement in day-to-day matters) and taking ultimate responsibility for monitoring

[141] Department of Health, Dublin (2001) *National Health Strategy ~Quality and Fairness, A Health System for You*. ISBN 0755711580.
[142] Copies can be downloaded from: http://www.healthreform.ie/publications/
[143] http://www.healthreform.ie/
[144] http://www.doh.ie/

and controlling service delivery. The reforms require a fundamental reorganisation of the Department to reflect these roles.

6.1.1.2 Health Services Executive (HSE)[145]

The HSE will run a single, unified health service with a new national headquarters and an estimated staff complement of about 300. There will also be regional structures that will enable the implementation of national policy at local level. This will ensure that patients will have equity of service across the country.

A Chief Executive Officer took up his position in April 2005. The HSE will have national directorates dealing with:

- Primary, Community and Continuing Care
- National Hospitals Office
- Population Health
- Change Management and Organisational Development
- Shared Services
- Finance
- Information Technology
- Human Resources.

6.1.1.3 Health Information and Quality Authority

A key policy aim of the Health Strategy is to deliver high quality services that are based on evidence-supported best practice. The Health Information and Quality Authority (HIQA) is being established to advance this aim. The Oireachtais approved the statutory basis for its establishment earlier this year.[146] The responsibilities of HIQA (and its structure) will be built around three related functions

- Developing health information;
- Promoting and implementing quality assurance programmes nationally; and
- Overseeing health technology assessment.

The primary aim of the National Health Information Strategy (NHIS) (launched in July 2003) is to recommend the necessary actions to rectify present deficiencies in health information systems. This is seen as essential to the successful implementation of the Health Service Reform Programme.

Other national agencies and companies with a relevance to research and services in the area of Pharmacogenetics include:

The Health Research Board,[147] is the agency responsible for promotion and funding of clinical research. It has a range of funding types available for research in hospitals and

[145] http://www.hebe.ie
[146] The full text is at: http://www.dohc.ie/legislation/statutory_instruments/pdf/si20050132.pdf?direct=1
[147] www.hrb.ie

universities on clinical research and on relevant basis research. It does not currently have a specific programme in Pharmacogenetics, but a few relevant projects are funded.

Other Funding programmes of relevance to PGx are detailed in section 6.1.5.

6.1.2 Hospital structure

In Ireland 86% of hospitals are public, 10% are private non-profit making and 4% are private profit making. They can be generally classified as:

- Health Service Executive hospitals, owned and funded by the Health Service Executive
- Voluntary public hospitals, most of whose income comes directly from the government. Voluntary public hospitals are sometimes owned by private bodies, i.e., religious orders. Other voluntary public hospitals are incorporated by charter or statute and are run by boards often appointed by the Minister for Health and Children
- Private hospitals, which receive no state funding.

All of the public hospitals will come within the control of the new HSE defined above. The basic statistics on the Public acute hospitals are in the table below.

6.1.3 Health cover

Healthcare funding is organised within two categories: medical cardholders, and cover for all other categories.

6.1.3.1 Free medical care:

Free Medical Cover is available to those holding 'medical cards' i.e.:

- Anyone under a specific income level, and their dependents
- Every person aged 70 or over
- Others with specific disease conditions, including some cancers.

Approximately 1.15 million people (32% of the population) were provided with free medical cover as of December 2004.

6.1.4 Private or state-subsidised healthcare cover

Those not within the free medical care net, can avail themselves of various health insurance systems. There is a state company Voluntary Health Insurance (VHI)[148] and two smaller competitors, including BUPA (Ireland). All employers provide the option of 'Group' insurance cover from one of these organisations. Participation in a group scheme has an additional cost benefit. All payments are also deductible from income

[148] see http://www.vhi.ie

tax. The insurance covers private care in hospitals (or as an outpatient in certain circumstances) or from various specialists in hospitals or in their practices. Payments are fully tax-deductible and subscribers can pay for whatever level of hospital care they choose.

6.1.4.1 Hospital cover:

At present everyone is entitled to hospital inpatient services in a public ward in all public hospitals. There is a €55 a night charge up to a maximum of €550 in any 12 consecutive months. These charges do not apply to medical cardholders. Higher rates apply for semi-private or private care.

6.1.4.2 Outpatient cover:

Attendance at the outpatients or Accident & Emergency (A&E) department of a public hospital, without referral by a General Practitioner (GP), may be charged at ∈55. There is no charge if referred by a GP. This charge does not apply to those with medical cards, or to those admitted to hospital as a result of attending its A&E department.

6.1.4.3 Drugs payment scheme:

Under the Drugs Payment Scheme (DPS) every citizen pays a maximum of €85 each month to cover the cost of prescribed drugs, medicines and appliances. The €85 limit applies to the total drug payments per household (i.e. spouses and dependant children). All costs above this amount are paid by the state.

Other forms of assistance, such as disability allowance, also apply in particular circumstances.

6.1.5 PGx research and service organisations

Since 2000, a major initiative has been implemented to develop Ireland as an innovation economy. This has involved a dramatic increase in R&D funding, with particular priority for biotechnology and Information and Communications Technology (ICT). The R&D funding available in the Current National Development Plan is €1.25billin. This funding will be made available through many state R&D funders, but particularly Science Foundation Ireland[149] and the Higher Education Authority. The latter agency runs the Programme for Research in Third Level Institutions (PRTLI)[150] which is providing €650m in capital grants for new R&D facilities and buildings.

Among the research activities that have benefited from this funding are several PGx-related projects and programmes. The major such initiative is the Programme for

[149] see www.sfi.ie
[150] http://www.hea.ie/index.cfm/page/sub/id/448

Human Genomics.[151] This is the major Irish activity of relevance to PGx. The facility has received €44m in capital funding from the PRTLI programme 9, €13.5m from Science Foundation Ireland 8, and has also benefited from funding from other agencies. It is managed by the Dublin Molecular Medicine Centre (DMMC),[152] which is a consortium of research organisations in molecular medicine. The partners include three Dublin colleges:

- Conway Institute – University College Dublin
- Institute for Molecular Medicine – Trinity College Dublin
- Biopharmaceutical Sciences Network – Royal College of Surgeons, Dublin.

This Programme aims to create a single Centre of Excellence in Molecular Medicine and Pharmacogenomics. Its goal is the application of human genomics and proteomics to the study of the pathogenesis, diagnosis and treatment of human disease. They run a wide range of programmes of relevance to PGx, which can be searched on the DMMC website.

The National Centre for Medical Genetics[153] provides a comprehensive service for all patients and families in the Republic of Ireland affected by or at risk of a genetic disorder. At the moment they do not have a specific research programme of relevance to pharmacogenetics, but they are involved in many projects to determine the genetic basis of disease, including:

- Genetics of autosomal dominant dystonia and Parkinson's disease
- Genetics of Rett's syndrome
- Genetics of Vesicoureteral reflux
- Genomics and proteomics of breast cancer
- Molecular Genetics of Tuberous Sclerosis.

Other Research Groups with activities in the broad area of PGX include Smurfitt Institute, Dept. of Genetics, Trinity College Dublin. This institute has several groups with activities of relevance.

- Ocular Genetics Unit: Genetic aetiologies of degenerative diseases of the human retina and development of gene therapy for such conditions.
- Neuropsychiatric Genetics Group: genetic aspects of neuropsychiatric disorders and traits so as to achieve better treatments and preventative strategies.
- Genable Ltd.[154] is a start-up company arising from research in this institute. It is involved in treatments for genetic disorders, but with an emphasis on gene therapy as the priority form of treatment.
- Surgen Ltd.[155] is a pharmacogenomics company established in 1998 and a subsidiary of the Royal College of Surgeons in Ireland. They specialise in cardiovascular pharmacogenomics, and also have more recent programmes in colorectal cancer, anaesthesia and epilepsy.

151 http://www.dmmc.ie/programmes.htm
152 http://www.dmmc.ie/about.htm
153 http://www.genetics.ie/
154 http://www.genable.ie
155 http://www.surgen.com/

6.2 Regulation of pharmaceutical and diagnostic products

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.

Pharmaceuticals: In fulfilment of this role, IMB carries out the following functions:

- Licensing of medicinal products for human use
- Licensing of veterinary products
- Licensing of wholesalers of human medicines
- Licensing of manufacturers of human and veterinary medicines
- Pharmacovigilance & Drugs safety monitoring
- Clinical Trial Licensing
- Inspection of wholesale and manufacturing sites

The IMB has recently appointed a staff member as the responsible person for Pharmacogenomics. However, as yet there has been no request by any applicant company for assistance in this area. The IMB is also not aware of any immediate product approval request that may require consideration as a pharmacogenetic product. The IMB plans to fully participate in EMEA policy discussions and other activities on the 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).[156] These regulations transposed into Irish law the provision of 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.

Medical Devices: The IMB is also responsible for regulation of medical devices and is the Irish Competent Authority. The National Standards Authority of Ireland (NSAI)[157] has been designated by IMB as the Notified Body in Ireland for general medical devices and active implantable medical devices. NSAI provides industrial and laboratory certification in a wide range of sectors. Since August 1994, NSAI has also been the Notified Body for performance of relevant tasks to ensure compliance with the Medical Devices Directive (93/42/EEC) and the Active Implantable Medical Devices Directive (90/385/EEC).

The NSAI was also designated by the IMB as a Notified Body for in vitro diagnostic medical devices (98/79/EC). The scope of this designation includes Annex II List A virology products, Annex II List B products and self test devices.

As in the IMB, there has been no request to NSAI for assistance and no initiatives have

[156] http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040878.pdf?direct=1
[157] http://www.nsai.ie/Certification_Services/Medical_Devices_CE_Marking/Medical_Devices.html

been started by NSAI in this area. They will be watching developments, but as yet do not see any demand for changes in their services or activities as a result of PGx.

6.3 Laboratory practice

Most Irish hospitals have historically had their own in-house analytical laboratories and there is currently no move to centralise such testing. At the moment there are laboratories operating within over 50 Irish hospitals. These would vary significantly in size and range of testing performed. Samples requiring more specialised testing are usually sent to the larger Irish laboratories, or to overseas laboratories.

Laboratory standards are monitored and assured in several different ways:

- Staff training and best practice in the different areas of laboratory practice (i.e. haematology, bacteriology, clinical chemistry, and immunology);
- Staff accreditation;
- Quality Assessment schemes.

The products used by the laboratories are also subject to a separate set of quality assessments.

6.3.1 Staff training and best practice

The Academy of Medical Laboratory Science[158] (AMLS) is the professional and academic body for Medical Laboratory Scientists in Ireland. It functions as the Designated Authority of the Minister of Health and Children, in evaluating the education and training necessary to practice medical laboratory science in Ireland. The AMLS is involved in running training courses, and in researching and advising on policies, procedures and technology relevant to maintaining quality within Irish medical laboratories. The Health Act (1970) specifies the qualifications required for medical scientists working in these laboratories. The Health & Social Care Professionals Bill (2004), which is currently in the final stages of approval within the Irish Parliament, will establish a formal council which will further regulate clinical biochemists and medical scientists.

The case-study PGx tests (HER-2 and TPMT) are more relevant to the area of clinical biochemistry. The Association of Clinical Biochemists of Ireland (ACBI)[159] is the national society for clinical biochemistry, and the Irish member society of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and of the European Communities Confederation of Clinical Chemistry (EC4). The ACBI is also the advisory body to the EC4 European Register for Clinical Chemists, which sets education and training standards appropriate for Clinical Biochemists at the higher professional level.

[158] http://www.amls.ie/profile.html
[159] http://www.acbi.ie/

The Association works closely with its sister organisations the Academy of Medical Laboratory Science and the Faculty of Pathology of the Royal College of Physicians of Ireland on issues related to the Accreditation of Irish Clinical Laboratories. It also runs conferences and other initiatives to promote the standards and quality of Clinical biochemistry practice.

The Irish Society of Human Genetics[160] promotes research and education for those professionally involved in human genetics and molecular medicine. Members are involved in research, education, clinical services and other professional activities. Their activities tend to be more involved in classical genetic testing rather than specific disease testing which has a genetic component (such as HER-2 or TPMT).

6.3.2 Laboratory accreditation

Laboratory accreditation is usually organised by the institution representing the clinical or scientific staff in the area of specialisation of the laboratory. At present many hospital pathology laboratories have adopted the Clinical Pathological Accreditation CPA (UK) Ltd Standard. These include:

- St Vincent's University Hospital, Dublin 4
- Cappagh National Orthopaedic Hospital, Dublin 11,
- Mater Misericordiae Hospital, Dublin 7,
- Our Lady's Hospital for Sick Children, Dublin 12,
- Beaumont Hospital, Dublin 9,
- St James' Hospital, Dublin 8,
- St Finbarrs Hospital, Cork.

The Bon Secours Hospital Cork Pathology Department has been awarded accreditation to the new International Medical Standard ISO/IEC 15189. This standard is based on ISO 17025 and ISO 9001 and provides requirements for competence and quality that are particular to medical laboratories.

6.3.3 Quality assurance

The Irish External Quality Assessment Scheme (IEQAS)[161] is a non-profit national independent scheme for the objective assessment of analytical performance in clinical laboratories. The number of participants increased from 33 to 50 (over 80% of all Irish hospital labs) between 1992 and 2000. The scope of the scheme also increased during this period from providing just clinical chemistry (14 analytes) to providing five schemes and 25 analytes for clinical chemistry.

A key role for IEQAS is the monitoring of performance. IEQAS has an established procedure whereby laboratories encountering problems are offered expert advice from the relevant Review Group (nominated from within the professional bodies). IEQAS has advantages over commercial schemes in that it is independent and therefore can use

[160] http://www.iol.ie/~ishg/
[161] http://www.ieqas.ie/

a variety of control materials.

Because of the small size of the Irish population, low levels of samples arise for some rare diseases. To ensure a quality standard, many of the Irish hospitals performing these tests participate in the UK National External Quality Assurance Scheme (NEQAS)[162] schemes, which covers a more comprehensive range of analytes. For instance, there is no QA scheme for HER-2 in Ireland, but the laboratories carrying out this test would be accredited to the UK NEQAS scheme. In relation to this test, it should also be noted that DakoCytomation provide training courses for users of their tests.[163] These involve both test performance and interpretation of results.

Those Irish laboratories which specialise in genetic testing are also members of the European Molecular Genetics Quality Network (EMGQN),[164] which runs QA schemes for some specific genetic conditions.

6.3.4 End user practice

This issue in Ireland is reflected in the comments of the other European case study countries. Pharmacogenomics could still be considered to be a research study in Ireland, and no major ethical or policy issues have arisen for those using the results of PGx testing. The Irish Cancer Society reports not adverse reactions by patients to the concept of genetic testing (see HER-2 Report) and a similar reaction is reported for Leukaemia patients.

Insurance and professional liability is a factor that is considered by the medical profession. A major factor for some clinicians in deciding to use PGx tests is the possibility of litigation in the event of failure to do so.

Life assurance members of the Irish Insurance Federation (IIF)[165] introduced a Code of Practice on genetic testing on 1st May 2001. The Code is due to expire on 31st December 2005. It has as its basis the established principles of fair treatment of all policyholders, and full disclosure of relevant material facts. The main provisions are as follows:

- Applicants may not in any circumstances be required to undergo a Genetic Test in order to obtain insurance.

- Disclosure of the result of a Genetic Test already taken by the proposer will not be required in new applications for life cover unless the sum assured on the new application exceeds €381,000 or if the total of the sum assured on the new application and other policies, if any, taken out with any insurer between 1st April 2001 and 31st December 2005 exceeds €381,000. This threshold is adequate to allow all proposers to obtain mortgage protection cover on the average home loan or to obtain a reasonable level of life assurance cover

[162] www.ukneqas.org.uk/Directory/services.htm
[163] http://www.dakocytomation.com/index/support_training.htm
[164] http://www.emqn.org/bp.php
[165] http://www.iif.ie

without the need to disclose previous test results.

- In the case of life cover exceeding this limit, and for critical illness and disability insurance, only approved tests will be used in the underwriting process of insurers.[166]

- A Genetic Test result disclosed by an applicant will not be taken into account when assessing a relative's insurance application.

6.4 Challenges regarding the integration of PGx into Irish healthcare

As yet, no specific policy positions on PGx would appear to have been defined by any national health agency on PGx.

The 1990 Report of the Committee to Examine Medical Genetics Services made no provision for cancer genetic services. However, the scientific developments underlying these services have mostly taken place since the report was published. A subsequent report on Genetic Services in Ireland in 1998 discussed the possibility that the National Centre for Medical Genetics should have a role in the provision of services in adult genetics, including hereditary cancer, but made no formal recommendations. The 1996 National Cancer Strategy, which refers to secondary cancer screening of those with cancer and the potential for screening families, also left unclear the role that should be undertaken.

There would therefore appear to be no overall policy position within the state as to the development or application of pharmacogenetics. However, there are clearly many examples of pharmacogenetic research, applications and other relevant activities.

Despite the absence of any policy references, there are no obvious barriers to the application and regulation of PGx in the Irish system. Agencies contacted were generally aware of opportunities in the area and interested to be made aware of developments. The low level of activity is a consequence of a low level of need for action.

At a research level, there is a reasonable level of expertise and activity. The major areas of research activity are more related to genetics of disease rather than genetics of therapeutic reaction. Nevertheless, there are relevant activities in the DMMC (see above).

6.5 Primary Sources

1 Official from: Health Research Board
1 Official from: Dept of Health & Children

[166] An 'approved test' is one that has been approved by the Genetics and Insurance Committee (GAIC) in the UK.

1 Official from:	Dublin Molecular Medicine Centre
2 Officials from:	Irish Medicines Board
1 Official from:	National Standards Authority of Ireland (Notified Body for Irish Medicines Board re Medical Devices Directive)
1 Official from:	Irish Cancer Society
1 Official from:	Irish Insurance Federation
4 Representatives:	Hospital Clinical Laboratories of which 2 are involved in Her2 testing and 2 in TPMT testing
1:	Consultant Haematologist
1:	Consultant Oncologist
2:	Representatives of Pharma and Diagnostic companies invoilved in PGx products

Chapter 7 The regulatory context of PGx in the Netherlands

Christien Enzing and Wieneke Vullings, TNO Innovation Policy Group, Delft

7.1 Structure of the Dutch health care system and expectations of PGx

As in several other European countries, the Dutch health care system is still based on a system of public and private insurance schemes. First, the Exceptional Medical Expenses Act provides the framework for a compulsory national insurance scheme for all residents in the Netherlands, covering chronic health care risks and catastrophic health expenditures. Second, every resident on an annual income below a yearly-adjusted specified level is compulsorily insured under the Health Insurance Act for normal medical expenses such as general practitioner services, hospital services and dental care. Third, people with an income above the yearly-adjusted specified level can take out private health care insurance.

Under the Health Insurance Act, health insurance companies enter into contracts with health care providers who are paid directly by the insurance companies without financial involvement of the patient. Privately insured patients have to seek reimbursement from their health insurers. In 2003, approximately 50 health insurance companies existed in the Netherlands.

In the Netherlands only pharmaceuticals prescribed by general practitioners and specialists are reimbursed. Not all pharmaceuticals are eligible for reimbursement. Moreover, the Netherlands operates a co-payment system in which patients are required to meet a part of the costs of their prescribed treatment; only a few pharmaceuticals are reimbursed in full. The Dutch government is not able to set prices for pharmaceutical products that are traded and prescribed in the Netherlands; this is the responsibility of the pharmaceutical companies. However, the Dutch government influences the price level by imposing very strict criteria for reimbursement by the public insurance schemes.[167]

PGx does not have a very high priority on the Dutch national agenda although already in 2000 a White Paper on the application of genetics in health care (De toepassing van genetica in de gezondheidszorg) was published. The character of the paper is rather descriptive; it gives an overview of the state of the art in the scientific field and about future developments. Also questions related to possible social and legal impacts and ethical issues are addressed. One of the main future activities presented in this paper is a public website on this issue, under the responsibility of the VSOP.[168] VSOP is an

[167] Enzing, C.M., van der Fiessen, A. and Kern, S. (2004) *OECD Case Study on Innovation: The Dutch Pharmaceutical and Food Biotechnology Innovation Systems*, TNO- Report STB-04-12, Delft.
[168] www.erfocentrum.nl

umbrella organisation of about sixty national, disease-linked, parent and patient organisations, most of them concerned with genetic and/or congenital disorders.

In the governmental Paper on Health Care, published in 2002,[169] the importance of genetics and genomics for health care issues is again recognised but no specific policy measures are mentioned. The VSOP, the Dutch Genetic Alliance, was very much worried about this. In a letter to the Minister of Health, VSOP asked for an integral government policy in this field because of the important role genetics and genomics will play in health care in the future. They request 'a quick implementation of early screening methods for specific genetic disorders and of applications of modern biotechnology such as farmacogenomics and orphan drugs'. They argue that the government is too slow in taking decisions in the field of modern biotechnology and genetics as it has announced that it wants to wait for reports to be published by the Council for Health Research (Raad voor Rezondheidsonderzoek – RGO), Council for Public Health and Health Care (Raad voor de Volksgezondheid en Zorg – RVZ) and the Foundation Futures of Technologies (STT). Recently, (mid 2005) RGO published, together with the Health Council of the Netherlands (Gezondheidsraad – GR) 'Annual Report on Genomics' (first edition published in 2004). STT did address genomics and health, but chose for the subject 'Nutrigenomics'. RVZ has not yet published a study on this subject (in 2002 they published the Paper on Bioscience and Policy).

One of the reasons for this half-hearted position of the Dutch government might be that there are hardly large national pharmaceutical companies present in the Netherlands and the one that are not there, are not yet active in this field, at least not in the Netherlands. So there is no strong push of industry, but only a weak pull from patients' organisations addressing the importance PGx innovation and issues related to PGx implementation. Compared to, for instance the UK, PGx is not a public issue, let alone a hype.

Also no specific PGx research programmes exist in the Netherlands. Part of the research financed through the National Genomics Initiative deals with health issues, but not specifically with PGx. The genomics research centres active in health research are the Centre for Medical Systems Biology, for the improvement of diagnosis, treatment and prevention of common diseases and the Cancer Genomics Centre that reveals the transition from healthy cell to tumour and aims to improve diagnosis and cure rates for cancer patients.

Recently an activity has been taken up to develop a plan for a Technological Top Institute Pharma; the program is still under developments. Pharmacogenomics could become part of it.

7.2 Regulation of pharmaceuticals and diagnostics

Market access of 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 the evaluation and issuing of market authorisations for

[169] Ministry of Health, Wellbeing and Sports (2002) *Zorg nota 2003,* Ministry of Health, Den Haag.

pharmaceutical products, including diagnostics, in the Netherlands. Their tasks are formulated in the Dutch Act on the Provision of Pharmaceuticals. CBG also determines whether pharmaceuticals will be registered, and whether they should be made available on prescription, or not.

Pharmaceutical products are evaluated on the basis of criteria that are 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. The Board also has the authority to contribute to and advice in the realisation of EU licences for the market introduction of medicines. The Board assigns the Dutch members of the European committee for pharmaceutical specialties: the Committee for Medicinal Products for Human Use (CHMP)

There are two alternative routes for authorisation of the pharmaceutical products:

- *The centralised route or procedure at the European level*. This leads to a marketing authorisation that is valid in all member states of the European Union. This centralised procedure is compulsory for market authorisation of all pharmaceuticals based on biotechnology techniques. The procedure starts with the application at the European agency for the evaluation of medicinal products – EMEA, which was set up in 1995.
- *The decentralised route or procedure*. There are two procedures possible: the national procedure and the so-called procedure of mutual recognition. The procedure of mutual recognition entails the recognition of a marketing authorisation provided by a member state of the EU by the other member states. To that end, the member state that issued the first authorisation provides their evaluation report to the other member states. The national procedure is used when the pharmaceutical company desires market authorisation for the Netherlands only or as a starting point for the procedure of mutual recognition.

Since 1.5 year EMEA has a pharmacogenetic working group. For the moment, as no PGx drugs development are at the approval stage, the EMEA working group is monitoring developments and is gaining expertise in this field.

The Dutch Pharmacovigilance Foundation (LAREB) is responsible for the assessment and registration of adverse reactions of pharmaceuticals, after market introduction.

Since 1993, the reimbursement of extramural pharmaceuticals has been regulated under the Medicines Reimbursement System (Geneesmiddelen Vergoeding Systeem – GVS). Under the GVS, the Minister of Public Health, Welfare and Sports decides, after consultation of the Board for Care Insurers (CVZ), which new pharmaceuticals are admitted to the public insurance schemes and become eligible for reimbursement. Moreover, the Medicines Pricing Act (Wet Geneesmiddelen Prijzen – WGP) gives the Minister of Public Health, Welfare and Sports the authority of setting maximum price levels at which pharmacists are allowed to purchase brand name pharmaceuticals in the Netherlands. The setting of such a maximum price level is based on the average price

level for the same active substance in the same therapeutic from in Germany, France, the United Kingdom and Belgium. This system of maximum price-setting has not contributed to the government's aim of cost-containment while retaining the quality of health care, as was hoped for. On the contrary, the maximum price-setting system stimulated a competition in pharmaceuticals merely based on margins rather than on the actual prices, leading to artificial high price levels.[170]

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 through a so-called 'General Rule of Management (Algemene Regel van Bestuur). The 'Decision In-vitro Diagnostics' (Besluit In vitro-Diagnostiek) was published in 2001. Diagnostic kits, such as the Herceptest™ of DakoCytomation, fall under the regime of this Decision. The fact that the HER-2 test can be used in relation to the prescription of a specific drug or not, did not give it a special status in this procedure.

Unlike in the USA, the market approval of the Herceptest™ of DakoCytomation and Roches Herceptin was not combined. The spokesperson of the CBG mentions that in the market approval procedure for Herceptin in 2000 this has been discussed, but because there were also other HER-2 tests in use, they did not want to exclude them (CBG 1). On the label of Herceptin the use of a HER-2 test was mentioned but not a specific one. So the demands of the CBG were focussing on the required level of protein expression when Herceptin had to be used and not on the test through which these levels had to be measured.

For several years, public health policies in the Netherlands have strongly emphasised cost containment. In particular pharmaceuticals, but also tests have been subject to cost containment measures such as the setting of maximum price levels, stimulating the prescription of generic pharmaceuticals and tolerating the parallel import of brand name pharmaceuticals. The continuously rising expenditures on health care in the Netherlands and its loss of quality also forced the Dutch government to introduce measures to deregulate the system and place more responsibilities at the level of individual actors within the health care system. The government acknowledged that cost containment had to be combined with measures that increase the effectiveness and efficiency of health care in the Netherlands. Therefore, the Dutch government decided in 2000 to commit the central role in the national health care system to the health care insurance companies, forcing them to take a more active role in the reorganisation of the health care system.[171] In addition, the system for determining the tariffs of intramural treatments has been replaced by the system of Diagnosis Treatment Combination (Diagnose Behandel Combinatie – DBC) that was introduced in January 2005. This system entails a specified price for a complete treatment of the patients, covering the entire process from diagnosis and hospitalisation to the discharge from the hospital.

[170] Enzing, C.M., van der Giessen, A. and Kern, S. (2004) *OECD Case Study on Innovation: The Dutch Pharmaceutical and Food Biotechnology Innovation Systems*, TNO Report STB-04-12, TNO, Delft.
[171] Enzing, C.M., van der Giessen, A. and Kern, S. (2004) *OECD Case Study on Innovation: The Dutch Pharmaceutical and Food Biotechnology Innovation Systems*, TNO Report STB-04-12, TNO, Delft.

7.3 Regulation of PGx products

7.3.1 Impact on existing regulation

The representatives from the government (MH 1, MH 2, MH 3, MH 4) and from the body responsible for admission of new drugs in the Netherlands (CBG 1) agree that the existing regulatory framework does not specifically encourage nor is a barrier to the development of PGx drugs or test.

For the Dutch health policies cost-benefits arguments are very important, so PGx leading to more effective drugs, with less side effects et cetera, makes them in principle very welcome, even when they are only applicable for specific groups. The spokesperson of the CBG says: 'we are very open for these new developments in the field of PGx and see no problems when it comes to regulation' (CBG 1).

According to one of the representative of the Dutch Ministry of Health involved in reimbursement policies, PGx drugs for stratified populations will not affect their approach, as these PGx drugs fall under the same regime as the orphan drugs (MH 1). Orphan drugs are only reimbursed if this drug has an exclusive status, meaning that no other drugs are available to cure these patients. The same would hold for a PGx drug for stratified populations. If a new PGx drug is an alternative for an existing drug, then cost-effectiveness arguments will be the leading principle for approval.

These PGx drugs will be very expensive and have to be reimbursed through the special budget for expensive drugs; which implies that maximal 75% of the costs of expensive drugs used by the hospitals could be reimbursed. But hospitals have only a limited budget which implies that not all tests and drugs that are needed to give optimal patient care can be used. Therefore patients that have to be treated with expensive drugs that is not provided by their hospital, go 'shopping' in other hospitals (that have not yet exceeded their budget) and even go abroad in order to get their treatment (see also the report with Her2 and TPMT case studies). As the Dutch reimbursement practice has a lot of weak spots, interviewees from the government expect that drugs companies are a little hesitant about the development of the group of expensive drugs such as PGx (MH 1).

In case extra skills and expertise for assessment of PGx drugs are needed within the Committee for Pharmaceutical Care, the Committee will have some extra new members that are specialised in the new fields. This committee advices to the Committee of Health Insurance Companies (College van Zorgverzekeraars) on including drugs in new reimbursement schemes. The Committee for Pharmaceutical Care has been growing in recent years as regularly new expertise was required; it now has 32 members (MH 1).

With respect to diagnostics, in the admission process (as set out in the 'Decision In-vitro Diagnostics'), a Conformity Assessment (Conformiteitsbeoordeling) has to take place. This implies that companies that want to introduce their new diagnostic kit on the national market have to send their dossier to the so-called 'Aangemelde instanties'. These are official test labs that are authorised for this task. For in vitro diagnostics there are two of these labs in the Netherlands: TNO and KEMA. The Ministry of Public

Health regularly monitors if these test labs have the necessary expertise to assess the tests. For the PGx drugs and test that are now on the Dutch market, no such extra skills and expertise was needed (MH 1).

7.3.2 New challenges for regulators

The persons involved in regulation of drugs that are interviewed see no specific challenges for regulators when it comes to market access of PGx drugs and tests; they fall under the existing regimes and these existing regimes are considered as functioning well (MH 1; CBG 1). The main criteria for market approval are safety and efficacy; and this also accounts for PGx. Most important criteria at the moment are the accessibility and 'payability' of Dutch health care. According to one of the Ministry's spokesman these criteria are at the moment more important then the quality of health care (MH 3).

However, there is one article in the 'Decision on in vitro Diagnostics' which has recently become under reconsideration. This is Article 2 that says that tests that are only used in one health care organisation (in the building in which is has been developed or adjoining properties) are under the responsibility of that organisation following the Quality Law Health Care Organisations (Kwaliteitswet Zorginstellingen). The test is not allowed to be delivered to other legal entities. This is also where companies like DakoCytomation that introduced the first Herceptest™ on the Dutch market, are worrying about and what now also has become an issue for the Dutch regulators. The Dutch case study reports on Her2 mentioned the complaints of this company about the fact that they have to have labelled products that fall under the Decision and that a number of what they call 'home-brewed tests' have no obligation of any kind: there are no requirements with respect to quality or safety and labelling is not required for these test. The quality of these tests is being questioned by the company. An interviewee of the Ministry of Health said that about 81% of the tests developed in such organisations are also used in these organisations, the rest outside and thus: not in accordance with the 'Decision' (MH 1).

The regulators now see that these practices are not in accordance with the objectives of the 'Decision'. For instance: patient material from one hospital is being sent to the hospital with the home-brewed test. The latter does the test and sends the test-results back. In this case the rules are broken because the home-brewed test should only be used for patients within the hospital that has developed the test. Second, a more general principle in Dutch health care policy is at stake, which is accessibility of the patients to the test (MH 1). Another principle being questioned relates to the commercialisation of the home-brewed tests. Article 2 was introduced in the 'Decision' in order to stimulate innovation. But what happens when an academic hospital files a patent on the test (as did for instance the Netherlands Cancer Institute with a breast cancer diagnostic test)? 'Are we happy with academic hospitals that make money' is a question now being under consideration by the Ministry of Health (MH 1).

This is, of course, also an issue for industry, as almost 50% of the tests used in the Netherlands are these home-brewed 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 about 40% of the laboratories in the Netherlands that do the IHC test, use the

Herceptest™, another 10% uses the Ventana test; the resulting 50% is home brewed. Company that bring her2 test on the market especially complain about quality control of the test (see WP2 Her2 Case study Netherlands).

A second regulatory issue (not so much a challenge) relates to the wider social and ethical impact of drugs like PGx. As values like 'the right for persons to decide on their health' (Zelfbeschikkingsrecht') is very important in the Netherlands, national regulators want the EU regulations to stay as lean as possible, only dealing with the minimal and basic values as safety, efficacy and quality. This gives them the freedom to fine tune and adjust the rules to national definitions and national values. In the Netherlands for instance, also private persons can decide about the use of a test or drugs, while in other countries only the health professionals are allowed to decide (MH 1).

7.3.3 Reappraisal of drugs through PGx tests

Reappraisal of drugs is a continuous process. It often happens that new indications for existing drugs are found which leads to new patents and thus to new approval procedures including reimbursement. Other reappraisal procedures deal with new dosages. Input for these reappraisals might come from post-marketing surveillance processes, complaints by patients and advices of doctors (in accordance with the systems of that is set up in order to monitor and report side-effects of drugs) (MH 2).

Most interviewees react very positive on the possibilities for the reappraisal of existing drugs and drugs that have not reached the market, through new PGx tests. The reason for this is that they might improve the efficacy of existing drugs and decrease negative side-effects. Industry must take the lead in this (MH 2; MH 3). The Dutch government is not very pro-active in this, even although it might be very cost-effective. There are some tendencies that the government position is chancing in this respect as there are now initiatives to monitor new developments in order to get a good overview. Furthermore, very recently the Ministry has formulated a biomedical research program, which is a sign that the Ministry wants to become a more active actor in this field (MH 3).

7.4 Regulation of clinical testing services

7.4.1 History of quality control in Dutch health care

Since twenty years, quality issues increasingly have gained a central place in the Dutch health care system. In the late eighties and beginning of the nineties, several societies for medical specialists have set up structural assessment procedures through mutual visitation committees. The Dutch government stimulated this development and organised a conference in 1989 in which all relevant stakeholders in the Dutch health care system were involved: doctors, patients, health insurance companies. The conference led to a number of recommendations that were discussed and reformulated during the following five years and finally were laid down in the Dutch law. The most

important laws address the professionals (BIG) and the care organisations (Quality Law Care Organisations- Kwaliteitswet Zorginstellingen).

Since 1995, Dutch laboratories in – or related to – hospitals and other places of clinical practice, have been active in the creation of an accreditation system for the guarantee and visibility of the quality of their processes and thus of the outcome of patient material research. In most case the Foundation for the Improvement of the Quality of Laboratory Research and for Accreditation of Laboratory Research in Medical Practice – CKKL (Stichting voor de bevordering van de kwaliteit van het laboratoriumonderzoek en voor de accreditatie van laboratoria in de gezondheidszorg). This Foundation has been set up by a number of professional organisations (such as clinical chemists, pharmacists, microbiologists, pathologists and immunologists). The systematic approach developed by CCKL is an implemented quality system that has been laid down in a handbook. The handbook provides a description of all relevant activities in a laboratory, the organisations, education and training of personnel, maintenance and calibration of technical facilities, the reporting of results, et cetera. The handbook includes all SOPs (standard operating procedures) that describe the main activities of a laboratory and that must comply with ISO 15189, an international standard for laboratories. The CCKL has implied this standard for the Dutch laboratories in its Practice Guideline (Praktijkrichtlijn).

Essential element in the quality systems are the annual audits of each of the laboratories by persons that have been trained for this. On the basis of a system of internal and external audits the laboratory should make a plan for further improvements and regular checks are practiced so the planned improvements are also being made. When a laboratory has been successfully passed through the audit it receives an accreditation for four years; after these four years it has again to pass the audit.

In 2005, achieving a CCKL accreditation is still not legally required. Laboratories do it on a voluntary basis since they want to comply with international standards. Being accredited or not, has no financial consequences.

For medical laboratories the CCKL developed a general framework for quality control systems. The clinical laboratories were the first to implement them, most pathological labs followed in the mid nineties. A next step was that the boards of a number of professional societies in pathology set up a quality office for mutual testing (external quality testing) of the technical quality of the tests done by the Dutch pathological labs.

7.4.2 Quality review in pathological analysis

In 1996 a working party ‘Quality Office’ developed the plan for the external independent quality assessment in clinical pathology that finally led to the Foundation for Quality Assessment Clinical Pathology – SKKP (Stichting Kwaliteitstoetsing Klinische Pathologie). Their credo was: quality has to be made demonstratable, it thus can be checked external and independent. In the working group were represented: the Dutch Society of Pathologists – NVVP (Nederlandse Vereniging van Pathologen), Dutch Society of Clinical Cytology – NVKC (Nederlandse Vereniging van Klinisch Cytologie), Organisation of Cytodiagnostics Workers – OCM (Organisatie

Cytodiagnostische Medewerkers) and Society Histotechnique Netherlands (Working Group Immuno Histocyto Chemistry) – VHN (Vereniging Histotechniek Nederland). The latter two later merged into the Society of Laboratory Assistants Pathology (VAP).

The goals of SKKP are primarily to keep the technological quality of laboratory work on a high level and second to review the applications and interpretations of national guidelines concerning laboratory work. SKKP does this through the organisation of so-called sendings of diagnostic tests (rondzendingen), presentation and discussion of results of these supplies and the development of criteria for reviews of diagnostics tests. SKKP replaces a number of already existing external review activities (QC 1).

SKKP offers all clinical pathological laboratories in the Netherlands the opportunity to join the sendings (process of external quality assessment). At the moment there are approximately 70 of these labs; most are part of or directly linked to a hospital, but there are also a number of independent labs that provide their services to a number of hospitals in their region (the Netherlands has approximately 100 hospitals, including the academic hospitals).

At the moment SKKP organises sendings in the field of histology, immunohisto-chemistry, cytology, cervix cytology and molecular pathology. The NVVP and VAP working groups advice SKKP each year on which specific test should be reviewed that year. Laboratories that participate in a sending, send their dossiers (test, test results and material) to other labs who check the test and write a short report. SKKP collects all reports, write a summarising and concluding document that is presented and discussed in a meeting with participants and other specialists. On the basis of the results of a review SKKP writes a report with recommendations. The NVVP can on the basis of this recommendation develop new guideless or adjust existing guidelines (QC 2).

Laboratories that want to participate in the review process have to pay an annual fee and for each test that is reviewed. Already from the start a high participation grade has been realised (more than 90%). Sendings are coordinated by two persons within SKKP; specialist working groups advice on the tests.

However, at the end of the day it is the responsibility of the individual pathologist to keep the quality level as high as possible. In the case of the HER-2 test the three pathologists of the Winschoten Pathology Lab did, before they agreed about the quality of their Her2 tests, a lot of tests on non lethal and lethal tumours and tests on material of which they already knew the results (P1). Other inputs in their learning process where literature, information from the cancer centres and national working groups of the NVVP. They also used the FDA report – that mentions the types of problems that can be met when doing the test – that was made in the approval process for the Herceptest™ of DakoCytomation. The pathologists also checked the outcomes of their test with the outcome of so-called reference centres, such as the university in the region that used another method. This internal learning process led the three pathologists finally to a point on which they agreed that they could conduct the test on the required quality level. Now they are involved in the SKKP sending of the Her2 test.

7.4.4 Code of practice: Secondary use biological

material

The FMWV is the Federation of Biomedical Scientific Societies and exists since the early 60's. It now comprises about 30 member societies (including NVVP) with all together 17,000 members. The FMWV annually organises a multi-disciplinary scientific conference with an adjacent public meeting. One of its main activities is to be a platform for self-regulation within the legal framework.

Two codes have been developed:

- The Code for adequate secondary use of data ('Gedragscode gezondheidsonderzoek met gegevens': Goed Gedrag)): this was developed in 1995 and has been revised in 2002 based on legal implementation of the European directive.
- The Code for adequate secondary use of tissue ('Goed gebruik'), developed during 1999-2001.

7.5 Challenges regarding the integration of PGx into Dutch healthcare

Already in 1999 the Dutch organisation for Technology Assessment, the Rathenau Institute, published a report on 'Predictive Health Care' (Voorspellende Geneeskunde). The authors of the report argued that the emergence of predictive medicine is accompanied by a number of issues that should be put high on the political agenda. Later, in August 2000, the National Health Council published a report on pharmacogenetics which also addressed issues like communication with the patient, the impact for reimbursement and the quality of the tests. The recommendations made in the report only led to a very short notice in the government report 'Genetics in Health Care' also published in 2000. The government report deals mainly with genetic testing and genetic counselling; new developments like PGx are only shortly mentioned in the 2000 report.

Today, interviewees from the Ministry of Health and CBG expect that PGx products will be introduced on the market, the coming years, especially diagnostics as it will take considerable more time before a new drug is developed and ready to be marketed. Expectations refer to diagnostics measuring interactions with drugs (for instance liver enzymes), side effects of drugs (for instance schizophrenia) and the efficacy of specific drugs (especially in oncology). The interviewees have observed that a lot of knowledge is now being developed in the field of pharmacogenomics and know that large pharmaceutical companies like Roche and GlaxoSmithKline are very active in this respect (Roche and Affimetrix have developed a chip for two types of enzymes that can detect the speed with which drugs are being decomposed in the body).

They expect that dramatic changes will take place in the pharmaceutical industry: blockbusters will no longer be the cash cows, new types of drugs will be developed and pharmacogenomics plays a crucial role in these new developments. One of the interviewees from the Ministry said: 'The consumer wants quality and PGx developments are one of the answers to this request' (MH 1). PGx will be a tool in

developing customised health care: for a more effective treatment with drugs but also for fine tuning of chemotherapies and even radiation.

Health care policy makers expect a better performance of drugs, so lower costs for national health care (MH 3). PGx can also be a tool in pharmacotherapy trails: detects side effects, monitor efficacy, fine tune dosages to patient characteristics, et cetera. Also PGx is expected to have impact on clinical trails as for instance dosages can be measured much more precise: on the whole, clinical trails will be more successful. The interviewees can not confirm that the promises of PGx are overstated (MH 1; MH 2; MH 3; MH 4; CBG 1).

Although these developments are rather attractive from a cost-benefit perspective, the Dutch government will not be a driving force in the development and implementation of these developments. They only actor that will be a driving force behind new developments in pharmacogenetic drugs and diagnostics will be the pharmaceutical industry according to a government representative. And as companies are still very reserved because of the small size of the PGx drugs market, uncertainties with respect to reimbursement and also ethical considerations, these developments are rather uncertain (C 2). The development of new diagnostic tools for a better fine-tuning of drugs to genetic, proteomic or perhaps even metabolic profiles, are considered as more realistic for the short term.

In the first 'Annual Report on Genomics, nr. 1' jointly produced by the Advisory Council on Health Research and the Health Council of the Netherlands in 2004, it is stated that the indirect application of pharmacogenetics is much broader, specifically in the pharmaceutical industry's selection of candidate medications. The direct application is only on a modest scale: in oncology and in the use of medications such as azathiopurine which is toxic to patients who are deficient in a specific enzyme that converts the medication (thiopurine methyltransferase). According to the report, the industry prefers not to develop drugs further when they are based on substances whose conversion varies sharply depending on genetic differences in the population. In the future, administering drugs to stimulate or inhibit disturbed metabolic and signalling pathways (directly or indirectly) will play a substantial role. Drug resistance is then translated into a matter of drug sensitivity based on previously defined patterns.

The Dutch government has, as has been mentioned before, been rather slow and not pro-active in this policy field. However, it is now in the process of getting an overview of the new developments and considering what the impact of new PGx tests and drugs can be and what role they can play. However, a PGx hype is not to be expected.

7.6 Primary sources:

Officials from the Ministry of Public Health, Welfare and Sports (MH)
Official from the College ter Beoordeling van Geneesmiddelen (CBG)
Representatives from the Stichting Kwaliteitstoetsing Klinische Pathologie (SKKP)
Representative from industry (IND)
Representative from a clinical-pathology laboratory (PAT)

Chapter 8 The regulatory context of PGx in the UK

Michael M. Hopkins, SPRU, University of Sussex and Graham Lewis, SATSU, University of York

8.1 Structure of the UK health care system and expectations of PGx

The UK healthcare system is characterised by a national system of provision, the National Health Service (NHS). Primary care is provided by GPs organised in local Primary Care Trusts (PCTs)[172] and secondary care provided by local NHS Trusts.[173] Wider strategic decision-making is the responsibility of larger Strategic Health Authorities (SHAs), and the Department of Health is responsible for funding and overall policy.

The Department of Health (DH) has an expert Advisory Group on Genetics Research (AGGR) for advice on genetics research as it applies to the DH and NHS. AGGR responsibilities include strategic oversight of DH genetics research and monitoring, co-ordinating and periodically reviewing the work of the Genetics Knowledge Parks.[174] It also advises on the DH Portfolio Director of Genetics Research on areas where additional research may be required to address the needs of the NHS and wider DH. The NHS is financed by direct taxation with delivery 'free at the point of need'. However, charges for certain services have always been levied (e.g. part payment for medicines, dentistry and eye care costs) and such charges have increased in recent years. The extent of private service provision is quite limited at this time.

In the context of PGx, the UK Government has recently sought to encourage the introduction of genetic services including PGx, as demonstrated by the 2003 Department of Health White Paper[175] which argues that:

> Genetics offers enormous potential to improve our health and healthcare – more personalised prediction of risk, more precise diagnosis, more targeted and effective use of existing drugs, new gene-based drugs and therapies, and prevention and treatment regimes tailored according to a person's individual genetic profile.

The White Paper aims to sets out 'a vision of how patients could benefit in future from

[172] *UK Health Act 1999* Available online at: http://www.opsi.gov.uk/acts/acts1999/19990008.htm

[173] A small but increasing number of such Trusts are independent of direct central government control – so-called Foundation Trusts.

[174] As part of the proposals set out in the 2003 Government white paper on genetics, six genetic knowledge parks were jointly funded by the Department of Health and Department of Trade and Industry to facilitate the exploitation of human genetic research.

[175] See Department of Health (2003) *Our Inheritance, Our Future – Realising the potential of genetics in the NHS*, Cm 5791. 24 June, The Stationery Office, Norwich. Available online at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/GeneticsGeneralInformation/GeneticsGeneralArticle/fs/en?CONTENT_ID=4016430&chk=RnGBgL

advances in genetics, and raise awareness of the potential of genetics in healthcare' and to take steps to 'prepare the NHS for introducing genetics-based healthcare into mainstream NHS services'. These goals were underpinned by a £50 million investment in new hospital and general practice services, with new laboratories, and education and training (including genetic counsellors). £20 million was earmarked for genetics research including £4 million for pharmacogenetics, to support research projects over a five year period starting in 2004, plus a further £2 million plus for related health services research.

The White Paper also set out 'safeguards and controls against inappropriate or unsafe use of developments in genetics'. In addition to existing controls on gene therapy and use of genetic test results by insurance companies, the UK government intends to 'introduce new legislation to ban DNA theft: it will become an offence to test someone's DNA without their consent except for medical or police purposes.'[176]

In recognition of earlier failures to gauge public reaction to new technologies, the Government also proclaimed the importance of public debate and openess and its intention to be responsive to new developments and shifts in public attitudes.[177]

The funding component for PGx research has been used to fund six studies:[178]

- The development of DNA-based screening for presymptomatic diagnosis of malignant hyperthermia
- Pharmacogenetics of GABAergic mechanisms of benefit and harm in epilepsy;
- Variability in response to warfarin: a prospective analysis of pharmacogenetic and environmental factors;
- A prospective randomised controlled trial of thiopurine methyltransferase (TPMT) genotyping in the management of patients, prior to commencement of azathioprine treatment;
- Pharmacogenetics of antimicrobial drug-induced liver injury;
- The pharmacogenetics of anthracycline mediated cardiotoxicity.

For the NHS, in the first instance, the areas of greatest significance are perceived to be adverse drug reactions (ADRs) and improvements of the efficacy of currently prescribed medicines, with a focus on those areas where PGx may have the greatest influence and utility, such as drugs that are commonly used and relatively expensive or used in otherwise healthy people. Another criterion is that projects are expected within 5 years of completion to 'lead to practical, and clinically acceptable, changes which are genuinely needed within the area of treatment.'
The current and ongoing PGx research programme highlights the promise that

[176] Department of Health (2003) *Our Inheritance, Our Future: Realising the potential of genetics in the NHS.* The Stationery Office, Norwich. Available online at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/GeneticsGeneralInformation/GeneticsGeneralArticle/fs/en?CONTENT_ID=4016430&chk=RnGBgL Accessed 16/05/05

[177] See footnote 172.

[178] Details on these key studies are available at http://www.genres.org.uk/prp/purpose.htm See also: http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4084217&chk=zuxPMw.

pharmacogenetics is relevant to the use of both existing and new medicines – in other words, the focus should not be solely on development of new, patentable, expensive medicinal products.

The drugs that are the focus for this research reflect those seen to represent the most potential given the existing evidence at present (DH 1). It is thought that the most immediate health benefits will arise from understanding the genetic component involved in ADRs or variations in efficacy in routinely-used generic products (DH 1). Examples include the anti-clotting agent, warfarin or psychiatric medications such as clozapine. Thus, according to the White Paper, there are:

> Potentially great benefits in identifying whether a medicine is only efficacious for people with a particular genetic make-up (genotype): non-responding patients can then be excluded from using the medicine. Alternatively, there are some medicines for which some patients are not non-responders, but have serious adverse reactions, leading to non-compliance with the treatment, possibly illness and on occasion death. Clearly avoiding prescribing such medicines to these individuals would be important: it is likely that for some of these medicines patients will have adverse drug reactions primarily as a result of their genotype, rather than any other factors.[179]

In March 2005, the DH announced further funding for research in genetics-based health services, aimed at

> consolidating and developing a robust evidence base to inform the policy, planning and implementation of health care services with a genetic element. This will include: the commissioning, organisation, management and delivery of services; and aspects of patient, public and societal attitudes and behaviour that may act as a driver for services and/or should be taken into account when designing them.[180]

The decision to fund PGx research with public money in effect recognises there is a lack of evidence on exactly where and how PGx can be, or should be, introduced into clinical practice in the NHS.

Other than the completion of the research projects detailed above, the DH does not expect much further impact from PGx in the short term. In the longer term the adoption of pharmacogenetics will depend, at least in the first instance, on how local hospitals prioritise the funding of these services (DH 1).

The cautious view on prospects for pharmacogenetics expressed by interviewee DH 1 is reasonably consistent with the more openly sceptical views expressed by laboratory staff of the utility of some early PGx hopes such as Cytochrome P450 and ApoE (Lab 1, Lab 2, Lab 4).

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[179] See footnote 172.

[180] Other current UK research relating to the factors influencing clinical introduction of PGx is being funded by the UK Economic and Social Research Council (ESRC) as part of its Science in Society programme (www.sci-soc.org.uk).
Also see http://www.york.ac.uk/res/pgx; and http://www.genres.org.uk/hsrp/call.htm

8.2 Regulation of medicinal products in the UK

Medicine regulation in the UK is the responsibility of the MHRA.[181] 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 is the case for other member states, it is not possible to review UK medicines regulation or the impact of regulatory activity on PGx developments outside the context of EU regulation.

Like several other regulatory agencies, the MHRA relies on 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 that exists in other member states in recent years.[182]

MHRA decisions are underpinned by scientific advice provided by an expert advisory committee, the Committee on Safety of Medicines (CSM) aided by several specialist sub-committees. Legislative measures to abolish the CSM along with the Medicines Commission (MC) and replace them with a new Commission for Human Medicines were introduced in April 2005. The changes will remove industry representation on the MC, and create several more expert working groups. Because of the growing complexity of drug development, the government also intends to introduce a greater degree of expertise at an earlier stage in the development process, and greater transparency, including increased lay representation.

8.3 UK regulation of PGx products

The following is predominantly based on interviews with two senior MHRA officials working in the regulation of drugs (MRHA 1) and diagnostics (MRHA 2).

8.3.1 Regulation of drugs

The main challenges arising from PGx drug development and clinical practice, according to a senior official at the MHRA, include the issue of ethics and sample storage arising from collection and storage of clinical trial samples; policy towards the possibility of 'orphan patients'; and labelling issues.

Pharmaceutical companies have routinely collected samples from clinical trials patients for several years and now have several million samples stored.[183] But such issues are probably not regulatory concerns, but reside within the wider society. Tension exists potentially between efforts to ensure privacy through sample anonymisation and

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

[182] In the USA, the FDA has been responsible for drugs and devices for many years.

[183] Lewis, G. (2004) 'Tissue collection and the pharmaceutical industry: investigating corporate biobanks', in Tutton R. and Corrigan O. (eds) *Genetic Databases: Socio-ethical issues in the collection and use of DNA*, Routledge: London, pp. 181-202.

regulators' need to maintain links to patient sources for safety reasons. There are debates also over the meaning and interpretation of informed consent (IC), and whether further consent is required for additional studies, possibly in the future when the science has 'moved on' and companies wish to test new hypotheses using stored samples.

Whilst recognising these tensions, it is probably wider society, not the regulators, who must find ways to resolve such dichotomies. If submitted data are scientifically valid, the MHRA is obliged to review them in the normal way. Similarly, from the regulatory perspective, the link to patients must be kept for all data submitted as part of the approval process. The EMEA has some initiatives in this area, and perhaps the EMEA has a role to play in developing a framework or guidance (perhaps through a third party) to overcome such dichotomies

The extent that the view of the MHRA agrees with that of the EMEA is not clear. The latter has stated that it is concerned with the issues of sample storage and IC. However, does this concern extend to competency, and if so, will member states and national agencies such as the MHRA accept this remains to be seen.

The MHRA is responsible for regulating clinical trials in the UK, and may receive data containing an element of PGx in one of two ways: data nested as part of the main study, or as a sub-set of patients included in a bigger non-PGx trial. Alternatively, the inclusion criteria for the trial may be a certain genotype.

There are several other issues that will require attention when more 'PGx products' seek approval and come on the market. One of these is labelling – what is put on the label, and how it is enforced. This relates also to development of a suitable diagnostic or 'kit' comprising the drug and in vitro diagnostic. Depending on the condition, this may need to be rapid and available 'near-bedside'.

Another topic that is of potential concern to UK regulators is so-called 'salami-slicing' or exclusion of patient groups from treatment because they possess the 'wrong' genotypic profile – also known as the 'orphan patient' scenario. There is concern that we could reach a situation where new drugs focus on certain groups to the exclusion of others for quite common conditions, such as hypertension for example. 'I think we have got to be very careful to provide a framework that doesn't disadvantage certain [people] because they don't happen to have the 'right' genotype' (MHRA 1)

This does not mean that a product directed at a particular population would not be approved. But it may impact on labelling requirements, if for example the genetic variation relates to metabolism, then it may be possible to overcome potential problems with advice on dosage. This may require the regulator to demand additional information from the sponsor if appropriate studies have not been conducted. Where this is not possible or where the variation relates to a pharmacodynamic effect and the product is directed at a specific population, adjustment of labelling instructions is clearly not possible and other measures may be necessary. In such cases, there may be a need to introduce commercial incentives to encourage development of products for such groups, much like existing orphan products legislation. 'If we go down the route of genetic medicine we have to find a way of providing incentives for minority populations' (MHRA 1). Parallels with this approach are drawn with recent moves by the EMEA and

FDA to ensure new drugs do not exclude the elderly and, increasingly, paediatrics. Such incentives would need to be introduced on a European basis.

8.3.2 Do existing frameworks encourage PGx development?

It was pointed out that there are a number of guidelines already existing that encourage the development of PGx related products and inclusion of PGx data in submissions. However, often companies do not use them to the fullest extent when developing products. The available guidance that is often not used includes the full investigation of different metabolic pathways, the relation between kinetics and dose response, bioavailability, and inclusion of foreign data.

The reasons for this situation are complex. In simplistic terms, it is the 'blockbuster versus targeted treatment' scenario, but in reality there are several elements to the issue. For example, if a company develops a highly targeted medicine directed at a given population, the risk/benefit ratio is lower, but the product is directed at a much narrower market, so the commercial incentives may be less. There are also re-imbursement issues which remain to be resolved. But the fundamental point, according to the MHRA, is that companies should apply the (at least) five guidelines that are available.

In practice, however, a pragmatic approach is adopted to such data requirements.

> At the end of the day, you look at the totality of the data and make a risk/benefit judgement, and no drug is perfect [...] It may be a question of in this population, some areas have been explored and some areas have not been explored. We have to be reasonably pragmatic. We want medicines and if we over-regulate we will kill off any medicines being developed. So we have to take a pragmatic approach in the end of the day. (MHRA 1)

Whilst this discussion refers to guidelines not legal requirements, and regulators assess MAAs on the basis of the complete dossier, they do have the power to require additional data if they decide it is necessary. If these guidelines are available, but are often not being fully utilised by industry, this raises the question as to whether regulators will, or perhaps should, in the future, routinely demand the full application of existing guidelines in the drug development process.

This topic relates to whether regulators are likely to routinely demand more PGx information in submissions. Information about pharmacokinetics and metabolic pathways is usually already required, but demands for routine genomics information, like that required in drugs targeted at specific populations, is not likely in the near future.

Decisions about what data to demand are ultimately a question of the risk/benefit of the drug. The MHRA official could certainly envisage a situation where, from a safety point of view, regulators start to collect genetic data from patients who do not experience ADRs, to evaluate whether those ADRs are related to a particular genotype, and we are likely to move to this scenario sooner rather than later.

8.3.3 Diagnostics

The implementation of the 98/79/EC IVD directive on in vitro diagnostic medical devices in 2003, and the ending of the transition phase in 2005, prompted particular concern in the UK as the NHS makes extensive use of 'home brews' in the area of diagnostics. The directive contains an exemption for 'reagents which are produced within health-institution laboratories for use in that environment'.[184] However the original MHRA interpretation of the IVD Directive was thought to suggest that NHS hospitals would not be able to offer services to other hospitals. Given the disruption to the health service such a situation would cause, the MHRA was forced to reissue guidance that extends their interpretation to allow continued offering of services between healthcare institutions even when these are discrete legal entities, given that the assay is not used outside of the lab of origin.[185]

Other than this concern, the view within the MHRA diagnostics unit is that they do not foresee any problems associated with introduction of PGx 'because we have a regulatory framework that is flexible enough to take into account any requirements of the tests' (MHRA 2).

Since the adoption of the IVD Directive, any company that wishes to market a PGx test in the UK must satisfy the requirements of the IVD Directive. This means that a test must do what it says it does, and the manufacturer must be able to support claims made for the test. The type of information required is performance, accuracy, precision and access. In other words, if a claim is made for 50% sensitivity, the manufacturer must demonstrate that this is the case, and if they do so, then the claim is accepted under the terms of the IVD Directive. It is then up to the person commissioning the test to decide if this figure is satisfactory for the intended purpose. In other words, there is no compulsion to demonstrate clinical utility, which is the responsibility of the physician to decide. The IVD Directive covers only safe use and performance, not clinical utility. If a proposed diagnostics meets the approximately ten criteria demanded by the IVD directive, the manufacturer can CE mark the product and place it on the market.

With regard to PGx, the MHRA interviewee did not believe there was likely to be a problem with the fact that clinical utility is not part of the diagnostics review process, unlike the procedure and requirements for the drug component of any PGx product.
There are four categories of diagnostic test under the IVD Directive. The highest category is reserved for products used to screen the blood supply, based on the fact that any problem is going to affect very large numbers of people. The second and third category (Self-Test Devices) requires less intervention. The fourth category is Self Declaration. Current PGx tests, such as the HER-2 test to determine whether to prescribe Herceptin for breast cancer, are subject to self-declaration.

For self-declaration, the manufacturer has to prepare a technical file for the product which lists how it has met the essential requirements of the Directive. The manufacturer then registers it with a Competent Authority in a Member State, which requires payment

[184] Directive 98/79/EC of the European Parliament and of the Council of 27th October 1998 on in vitro diagnostic medical devices, page 1.
[185] Berg, J. (2004) ''MHRA climb down on in-house assays', *ACB News*, August, pp. 4-5.

of a fee for the CE mark and then places it on the market. The MHRA has a Compliance Unit that investigates Adverse Incident Reports, or if an informant alleges that a test does not meet the claims made for it. In this case, the technical file is called in and the Unit will asses the data to see if they meet the claims being made by the manufacturer. According to the MHRA:

> Even though a product is self declaration, there is a well established mechanism for investigating potential non-compliance […] It's [the product] has got to do what is says it does. So if you've got the HER-2 test – that's a well established one – you've got to show that it measures HER-2-neu. (MHRA 2)

> …before the manufacturer can put it [the PGx test] on the market it has got to prove that it does that. It says it measures HER-2-neu, so somebody prescribing the drug (Herceptin) is then got to look up: right I've heard there is this link between HER-2-neu and Herceptin, I am going to measure it and there has got to be a body of evidence there but that respect, of linking one to the other [i.e. clinical utility] isn't covered by the IVD Directive. The IVD Directive covers the performance of the test. (MHRA 2)

The interviewee did not feel there was any difference between PGx tests and other diagnostics tests with regard to demonstration of utility, such as to warrant demonstration of clinical utility.

> I don't see that PGx is any different than any other Dx test because you would want any Dx test to be clinically useful. What the IVD Directive does is essentially establish a Single Market for diagnostics across the EU, with tests meeting a stated performance. It is then up to the person commissioning, allowing it to be used, to ensure that that test meets their requirements. They must make an informed decision on whether or not the test meets their needs, based on the information provided by the manufacturer, and whether or not that test meets their required performance, by 'increasing their awareness of what the test can, or indeed, can't do, for them. (MHRA 2)

What is clear is that present EU arrangements, as provided in the IVD directive, do not require any guarantee of clinical utility, only laboratory performance. Issues such as test performance and utility within different populations and interpretation of test results are not addressed.

8.3.4 A regulatory perspective on expectations of PGx and its impact on product regulation

It was felt that the promise of PGx was generally over-stated (although of course, the answer to this question depends on what is meant by 'over-stated'). The considered view is that whilst we can expect a few more PGx products to be marketed over the next 5-10 years, some of the wilder claims about 'personalised medicine' and major changes to medical practice are unfounded. Change to a more genetics-based medicine will occur, but the change will be incremental and take a much longer period to happen. We can expect some more pharmacodynamic-based products based on genomics, but the

sort of switch to personalised medicine that some commentators envisage is not going to occur for at least 15 years and maybe more (MHRA 1).

Some observers have argued that there has been an imbalance in the effort expended on improving pharmacovigilance compared to drug development for a number of years in the EU. The projected reduction in the number of individuals required for Clinical Trials (CTs) with stratification according to response, PV becomes very important, with some scientists arguing for post-marketing collection of genetic data, perhaps linked to the concept of provisional approval.

PGx products will require a diagnostic to be developed in tandem or to utilise an existing product. From a regulatory perspective, the potential problems around joint development are 'not insurmountable'. Clearly, the diagnostic element has to be appropriate, and validated, accessible, and rapid if the indication demands that an immediate answer is required. However, appropriate development and matching the drug and a validated diagnostic are possible.

Assessment is expected to be a package, with Herceptin providing a good example. The asymmetric position in Europe where drugs are approved by means of a European approval system (either centralised procedure or mutual recognition) whereas diagnostics are approved at the national level, does not present insurmountable problems. 'It may not be the smoothest way of doing things [...] but it happened with Herceptin [and] I don't see why it cannot happen with other things' (MHRA 1).

Larry Lesko and Janet Woodcock, both senior FDA staff, have previously raised the possibility that increased availability of PGx data might provide the impetus for regulators to re-review products already on the market – a policy that would be likely to raise concerns for industry, and for regulators also, but one that could benefit patients.

The MHRA believes that there must be a trigger for the re-reviewing of drugs, and it would normally be a safety issue. If there is a concern about safety, and if new data suggest this or sheds light on a safety issue – or more accurately, on the risk/benefit, then this is a very good reason for going back and reviewing old drugs. However, in the absence of a particular issue, or if the data do not make a difference to the risk/benefit ratio, it is unlikely that regulatory agencies would re-review old drugs, not least for resource reasons. In cases where re-review did take place, this would be conducted at the same level as original approval took place, with appeal to the CHMP.

The MHRA also believes there will be increased use of the centralised system for PGx products, but arguably this trend will merely reflect the general trend to use this procedure more frequently.

The MHRA also fully supports introduction of the 'safe haven' concept and 'Briefing Sessions' for early discussion of PGx data by sponsors and EMEA regulators .

8.4 Regulation of clinical testing services

Regulatory licensing of products (drugs and kits) operates within the regulatory

framework set out by the MHRA and relevant EU directives. While drug prescription is controlled by clinicians and pharmacists, in theory there is nothing to stop 'anyone' from establishing a testing service. In practice however the use of diagnostics occurs mainly within the NHS and clinical users of laboratory services abide by local and professional guidelines, with peer oversight playing an important role in assuring compliance in the absence of strict policing (DH 1, Lab 3, Lab 6).

As such the use of PGx related information is likely to be influenced by many groups within the NHS. However, formal legislation is not the primary mechanism for this regulation (DH 1). Therefore here we take a broader view of regulation, which includes the following:

- Research laboratory and clinical laboratory practice
- Quality assurance schemes in service laboratories (including PGx services)
- Accreditation schemes
- Clinical guidelines issued by professional bodies and national frameworks.

8.4.1 A role for research and clinical lab staff, and their professional bodies

As new genetic tests emerge NHS clinical staff have traditionally relied on 'home-brew' tests developed by public sector laboratories. Typically commercial organisations enter the field and develop kits as the science matures and markets become more clearly defined. As a scientific field matures hospital pathology departments inject funding into dedicated clinical laboratories as the benefits of testing are demonstrated to Hospital Trusts through presentation of a business case by testing labs and lobbying by local clinician customers.

There are relatively few laboratories offering PGx testing in the UK beyond the services related to cancer drugs such as Glivec and Herceptin (DH 1). Some might expect PGx testing to fit within the existing structures for genetic testing services for rare inherited diseases which are generally supported by allocation of contracts by service commissioners located within PCTs in the UK (although this is likely to change soon) at local or regional levels. However, at present it seems those concerned with genetic testing for heritable conditions are likely to be extend their remit to include pharmacogenetic services (personal communication – UK Genetic Testing Network)..

In terms of the provision of testing services, clinicians within the NHS may obtain laboratory tests for genetic traits including PGx related information from a laboratory (NHS or otherwise – although their choice of laboratory may be constrained by service agreements made by their hospital). The clinician retains ultimate responsibility for interpreting the information revealed by such tests. At present PGx services are provided to NHS patients by research labs, dedicated clinical labs and private pathology labs (Lab 2, Lab 3, Lab 5). In general it appears that labs offering HER-2 testing services do not have experience of offering testing for inherited genetic diseases although they may be involved in developing services for more than one kind of PGx test such as that for oestrogen receptor testing for use with Tamoxifen (Lab 5, Lab 6). Laboratories offering TPMT testing more commonly offer tests for inherited conditions (Lab 1, Lab 3). These labs are not affiliated with the UKGTN, perhaps because they

generally offer genetic tests using biochemical methods rather than molecular genetic methods. It is not thought that any dedicated molecular genetic testing labs from the UKGTN labs offer pharmacogenetic testing services at present (Lab 4).

Dedicated clinical labs tend to develop their own testing methodologies especially those laboratories with research links, entrepreneurial staff with enquiring minds and access to sources of capital such as local charitable foundations or cross-funding from existing budgets. The services that emerge are based on local laboratory interpretation and evaluation of published methods and the resources available to hand, allowing adaptation, as well as original methods which some centres are able to develop. This pattern appears to be consistent between labs undertaking services for HER-2, TPMT and rare genetic diseases.

An important difference between research laboratories and clinical laboratories is that staff training requirements are very different. In research laboratories technical staff taken on to perform tests are often graduates or postgraduates trained to masters level. They receive on-the-job training in the manner of an apprenticeship. However clinical lab staff with responsibility for service testing generally undergo a two year structured training programme and examination. Senior staff may have to pass an extensive set of exams to become a member of the Royal College of Pathologists, and technical staff must be state registered Biomedical Scientists if they are to work unsupervised in the laboratory (indeed this is the case for both NHS and private laboratory staff as required by the CPA standards – see section on accreditation below). The schemes for this training differ between lab disciplines, and their organisation is often an important role for the relevant professional body. However in the early years of a new sub-specialty a relevant professional body may not have emerged and existing bodies, such as the Association of Clinical Biochemists, which those offering biochemical based genetic testing services may belong to, would have more wide reaching obligations and might not be focused on the needs of those providing specialised services with distinctive needs (Lab 4).

8.4.2 Quality assurance schemes

Historically, as services mature there has been an increasing pressure to provide 'audit trails' and ensure quality of service is improved. However since the 1980s in the UK there has been additional peer-group pressure and user/payer-led pressure for laboratory services across the NHS to establish formal QA schemes. This is part of a growth in QA schemes across industry in general that may have arisen in part from OECD initiatives in the early 1980s to promote good laboratory practice in the assessment of dangerous chemicals, including formal mechanisms for peer assessment.[186] In clinical practice these schemes are supplemented with advice and best practice guidance from professional bodies (for example the Clinical Molecular Genetics Society) – indeed such informal systems often pre-date the formal QA schemes. Schemes established by professional bodies are often good at stimulating convergence in practice – such as selection of similar methodologies.

[186] For the OECD principles of good laboratory practice see 'Council decision on the mutual assessment of data in the assessment of chemicals' and associated 1997 amendments at www.oecd.org

At present QA schemes in the UK are co-ordinated by independent bodies such as NEQAS Ltd., that advise specialists in the field on how to more formally and anonymously appraise the performance of their colleagues.[187] NEQAS offers impartiality and cross-disciplinary experience of QA management for organisers. As a trusted third party, they can also annoymise test reports if necessary. They also facilitate discussion and transparency and even meetings of the testing community within a scheme. QA schemes tend to be test specific – so diligent laboratories will find themselves involved in a number of QA schemes if they offer a range of tests.

Externally run QA schemes for laboratories generally assess performance at regular intervals. These vary and may be monthly, quarterly or yearly depending on the specific service and scheme. The QA process involves the distribution of samples from an organiser to participants, who return their analytical results for examination by the organiser (Lab 3, Lab 4, Lab 6). In some schemes, particularly those for inherited diseases, the interpretation applied to results as reported to physicians is also examined, and in the case of HER-2 testing in the UK, the participants send the samples they have prepared and stained for examination as well (Lab 6).

Schemes organisers are also increasingly developing more sophisticated additional procedures such as online surveys to gather details of the methods used by participants in an effort to correlate poor performance with particular practices (Lab 6).

Membership of a QA scheme is educational and proven to improve error rates, however despite its increasing popularity users and organisers have highlighted weaknesses in the QA system:

It may be difficult to compare different methodologies, and when opinions differ over a result in a nascent diagnostic field, for example over where to draw the boundary between low metabolisers and normal individuals (given that a normal distribution is seen in the population as a whole – not tri-modal as originally thought) who can say who is doing the right thing or has the right answer? Harmonising practice through QA schemes is important in the development and use of protocols but they cannot force laboratories to follow their recommendations – they can merely guide labs (Lab 4). Although in theory continued failure to heed QA scheme warnings on performance can lead to withdrawal of participants from the scheme with implications for that lab's accreditation status, in practice it was noted by one lab that QA schemes 'do not have teeth' (Lab 5). Lab staff also inevitably take more care over the processing of samples sent by the QA scheme organiser than those that are sent for routine analysis (Lab 4). The non-profit making basis of QA schemes also means that the organisers do not always have the money to invest in new systems to be able to evaluate them effectively (Lab 6).

There are barriers to some labs joining schemes and these include professional rivalries; differences in patterns of working within a community of testing labs, for example reporting practice can differ with some labs favouring the provision of clinical advice or

[187] NEQAS is one of several such organisations providing quality assessments, but others such as WEQAS and Randox also operate in the UK (Lab 3).

interpretation and others not. Resource limitations such as staff time were cited as being a problem for smaller labs.

There is concern that the impact of difficulties in the QA schemes is likely to be magnified as accreditation becomes mandatory (see below). As noted above if labs do not have membership of a QA scheme where one is available, this can lead to failure to obtain accreditation (see below). If this occurs then it may have implications for the wider department (Lab 1).

The relative positioning of the QA schemes in the wider context has implications for its utility. For example in HER-2 testing, the QA scheme was able to be built up rapidly following from the strong support that Roche and Genentech gave to the infrastructure for HER-2 testing in the UK leading up to the launch of Herceptin,. Thus a strongly co-ordinated professional advisory body was already in place (Lab 5). This group has published successive guidelines outlining best practice[188] and helped to co-ordinate the efforts of a joint working party between the Royal College of pathologists and the NHS breast screening programme (Lab 5, Lab 6).

Nonetheless their recommendation that labs should only operate if they undertook more than 250 tests per year will be difficult to enforce as there is little incentive for labs to comply. This is unfortunate as the Oestrogen receptor QA schemes demonstrated that many labs operating at low scales have poorer performance due to inexperience with test methodologies (Lab 5).

Despite the above limitations, overall the UK has historically been an innovative early mover in the area of accreditation schemes. As such there is an increasing tendency for QA schemes established in the UK to take in participants from abroad, the EMGQN being one example within Europe. Even though PGx QA schemes are relatively new, the TPMT pilot QA scheme established in 2003 in the UK has 11 members worldwide, and 11 other interested in joining. The UK HER-2 QA scheme founded in 2000 has over 300 participants across Europe. This activity hints that QA schemes have themselves become a market – not least because providers need to spread their costs to make schemes affordable.

8.4.3 Accreditation

In recent years QA scheme mechanisms have been complemented by accreditation schemes. UK pathology laboratories are now encouraged to obtain accreditation from Clinical Pathology Accreditation (UK) Ltd.[189] or the UK Accreditation Service (UKAS) (the latter have a broader remit and their scheme members include engineers and non-diagnostic labs). By 2006 laboratories will be required to have registered with one or both of these schemes, although they will not have to have achieved full accreditation (Lab 3). Since 2002, these two bodies have been working together to align their

[188] See Ellis, I. Bartlett, J. Dowsett, M. Humphrys, S. Jasani, B. Miller, K. Pinder, S. Rhodes, A. and Walker, R. (2004) 'Updated Recommendations for HER-2 testing in the UK', *J. of Clin. Pathol.* Vol. 57, pp. 233-237.
[189] http://www.cpa-uk.co.uk/ accessed 23/1/05

accreditation scheme objectives.[190] Nonetheless a trend towards CPA accreditation is perceptible to some in the field. This may be because the CPA is overseen by the Royal College of Pathologists. Furthermore UKAS accreditation is on the basis of individual procedures conducted by a lab (so individual services may be approved), while clinical pathology accreditation covers the whole portfolio of a laboratory's activities, including any new services developed subsequently.

Both CPA and UKAS are based on internationally recognised standards such as ISO 9001 and 9002 quality management schemes, as well as the new (2002) schemes – ISO 15189, specifically for medical labs, ISO 17025 on calibration.[191] Indeed the CPA regulations follow these to the letter – their wording in places is identical (Lab 4). CPA visits labs for inspection on a 4-year cycle, which is less frequently than its counterparts in the USA, for example. Accreditation is sought at the departmental level, but where pathology departments consist of several laboratories, each of these will be inspected and the failure of one lab may have implications for the overall departmental accreditation (Lab 1, Lab 3). CPA rules cover a range of quality measures from how laboratories undertake and record their standard operating procedures (SOPs) to how much working space and how many staff they require, reflecting the Good Laboratory Practice guidelines. More recent CPA guidelines detail how new tests should be validated prior to use and indeed even commercial kits need to be validated for local use (in genetics in particular this means investigating whether the kit will work reliably given the genepool of the local population). This may inhibit innovation in laboratory practices by smaller labs, as the setting up of new tests will require more resourcing. It should also be noted that laboratories engaged in 'working up' new tests seem to be less familiar with these guidelines than might be desirable, although they suggest that the processes they apply, including the trial of a new method against several hundred samples, would be recognised more widely (Lab 1, Lab 2).

Although there is a concerted effort in the NHS at present to move towards accreditation as the norm, it has been suggested that the NHS cannot afford to upgrade facilities for many laboratories to enable them to pass CPA. With little spare testing capacity in the system, rigorous enforcement of the CPA system is viewed as unlikely for the time being so labs are unlikely to be prevented from continuing to offer services as long as they are seen to be attempting to improve (Lab 6).

8.4.4 The CE mark

Despite the exemption provided to clinical labs by the MHRA's interpretation of the IVD directive (see section 8.3), clinical labs may consider participating in the CE review process to get an internally produced assays approved. Notably NHS labs increasingly behave like commercial entities and they expect the CE mark to provide added value to their services.[192] A kite mark brings these labs onto a level playing field with industry kit producers in terms of the regulatory burden on product quality and may open up opportunities for these laboratories to provide services to industrial

[190] http://www.cpa-uk.co.uk/ accessed 23/1/05
[191] see http://www.iso.org/iso/en/ accessed 7/4/05
[192] Berg, J. (2004) 'MHRA climb down on in-house assays', *ACB News*, August, pp. 4-5.

partners.

In the UK the CE mark is administrated by the MHRA. Clinical laboratories wishing to apply for a CE mark on their assays and the service they are used to support must provide the following evidence of competency in a technical file (equivalent to about 4 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 to minimise failures have been implemented
- Reagent manufacture controls – best before dates and audit trail
- Vigilance system – processes to ensure errors are detected
- CE declaration of conformity.

One laboratory to have undertaken this process reports that this process was time consuming, but the experience would not put them off applying for further CE marks on their other assays**.** They suggest that previous concerns of laboratories that the IVD directive would restrict their ability to operate in the future may have been unfounded. Furthermore the process of internal risk assessment in particular, that is undertaken as part of the process, has led to a number of significant in-house improvements to their service, including data links between instrumentation and computer systems to automate data 'transcription' from one system to another and thereby reduce opportunities for human error and improved speed of reporting (Lab 3). It may be that although the CE mark was not intended to be applied to NHS laboratories, its application here could have an impact on the robustness, both in terms of quality and delivery, of such services.

Some have noted that there appears to be a regulatory gap in the provision of diagnostic testing services in that 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). Furthermore even when kite marked kits are used by laboratories, there is nothing to prevent the laboratories from deviating from the protocol. For example in the testing of HER-2 there are still sources of local variation. Lab staff in different centres use different preparation methods because they find methods suggested in the kit's instructions are not those they are used to. Sample retrieval methods used by clinical staff prior to the samples arriving at the lab are also variable (Lab 5). Furthermore due to the cost of kits there 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 schemes results (Lab 5).

8.4.5 The clinical use of PGx data

So far we have examined mechanisms that regulate the use of PGx tests in the laboratory. Here we examine the mechanisms that exist in the UK to regulate how that

information is used by clinical staff, beginning with the transfer of knowledge from the lab staff to the clinical staff.

The distribution of the interpretive burden is markedly different between PGx test applications, and also differs from the reporting of genetic tests for rare disease. In the latter cases, typically a high level of interpretation may be provided for non-expert practitioners, and it is often felt that best practice is to prepare a report that is clear, to reduce chances for misinterpretation perhaps by a non-specialist, on the grounds that one never knows who will end up reading it (Lab 4). However at the other extreme, some laboratories provide the minimum of interpretation because they serve only one specialist discipline (haematology being an example). In the case of research laboratories, staff are not qualified to provide clinical advice on how to interpret results. In the case of TPMT samples tested in clinically accredited laboratories it seems that staff do not always regard it to be their responsibility to educate their users, however they are concerned that they may not be making best use of the test results and often do talk to their customers on the telephone. For others education is a higher priority but at the same time they are cautious of being accused of drumming up business.

In the case of HER-2, the interpretation of test results falls on the breast cancer consultants. Cancer treatment in the UK has recently been re-organised into local networks, which meet sometimes weekly. Pathologists attend these meetings and this provides an opportunity to engage in discussion of tests results directly. Such arrangements are reportedly part of NHS policy to encourage interaction and improve accountability (Lab 6).

While the clinical user has ultimate responsibility for interpreting the results of the tests they request, their professional bodies also provide best practice guidelines to aid them. In the field of pharmacogenetics it appears that such guidelines are only just beginning to emerge and they appear to do so unevenly so that while one discipline such as the gastroenterologists might remain unconvinced of the utility of a PGx test of TPMT, others such as the dermatologists may recommend it as being essential prior to the commencement of treatments (Lab 3). Likewise there is variation within disciplines as some individuals are more inclined to keep up-to-date than others. At the policy level variation in uptake is seen as part of the normal, although undesirable, process of knowledge diffusion (DH 1). At the laboratory level, where a pharmacogenetic test for drug metabolism is all too often only requested post-hoc, staff are more familiar with the implications of uneven clinical uptake and greet this with frustration:

> If you are treated with 2.5 mg per Kg of azathioprine and you haven't got the enzyme, the result is going to be the same for you whether you saw a dermatologist, a rheumatologist, a haematologist or a gastroenterologist…you will end up in a hospital bed, on ICU [intensive care] or worse. (Head of Lab 3)

Lab1 suggested that a limiting factor for take up might be that the hospital that pays the cost of the test is not the same hospital as the one that may bear the cost of an adverse drug reaction (other than TPMT testing for Acute Lymphoblastic Leukaemia (ALL), because both mylosuppression and leukaemia might be expected to require the intervention of haematologists), and some agreement with this view was forthcoming from the DH interviewee. In the case of TPMT testing this may prove especially

problematic because over 300 tests might be required before a TPMT deficient patient is detected (Lab 1). While for the health service and society as a whole the cost benefit of TPMT testing is reasonably clear,[193] for the physician at the department level, especially where thiopurine drugs are less frequently used, it may not be seen as a relevant expense because of the rarity of such events in their experience.

Indeed personal experience of a patient with an ADR seems to be one of the main motivations for clinicians to use PGx services (Lab 1, Lab 2, Lab 3), and as such patterns of uptake can be expected to be idiosyncratic. Although some laboratory staff make efforts to advertise their services, this is perhaps less common than it could be, and clinical opinion leading on the subject appears to be at a relatively early stage.

While in other countries more formal legal frameworks might guide the adherence to particular modes of clinical practice, the UK system relies on a number of bodies which act as 'levers' which influence clinical behaviour rather than legislation (DH 1).

8.4.5.1 The National Institute for Clinical Excellence[194]

The National Institute for Clinical Excellence (NICE), which recommends whether approved products can be purchased by the NHS is often referred to as the 'fourth hurdle'. NICE was set up as a SHA in 1999 with the objective of improving the quality of care NHS professionals provide to their patients. Because NICE is required to consider both clinical as well as cost-effectiveness issues in formulating advice, its role and guidance are often controversial.

NICE has a role in reducing the variability of practice in the NHS in England and Wales, by providing evidence-based guidelines. While it cannot require clinicians to abide by these, it can insist that NHS fund holders provide reimbursement for approved therapies/procedures. Funding bodies are required to review their practices in the light of NICE guidance.

Existing PGx products such as Herceptin and the HER-2 test have been recommended for NHS use by NICE. However, when compared to the US case, for example, the NICE recommendation for use for the approved indication occurred many months after regulatory approval and use.

8.4.5.2 The Health Technology Assessment Programme (part of NHS R&D)[195]

This is a programme of research that aims to build the evidence base in various fields

[193] Winter, J. Walker, A. Shapiro, D. Gaffneys, D. Spooner, R.J. and Mills P.R. (2004) 'Cost effectiveness of thiopurine methyltransferase genotype screening inpatients about to commence asathioprine therapy for treatment of inflammatory bowel disease', *Aliment. Pharmacol. Ther.*, Vol. 20, pp. 593-599.

[194] http://www.nice.org.uk/ accessed 23/01/05

[195] http://www.hta.nhsweb.nhs.uk/ 23/01/05

through provision of new evidence or reviews of developments in a technical field so as to provide an assessment of best practice and cost effectiveness.

8.4.5.3 National service frameworks (NSF)[196]

NSF is an initiative that provides guidelines for how services should be provided and informs patients what they should expect of a service. These are prepared for practitioners by practitioners and are of particular importance in primary care. Examples of NSFs' focus include diabetes, mental health, children, long term illness. These are frameworks focused on providing guidance on the complete range of service-related considerations for specific groups of patients.

8.4.5.4 British National Formulary (BNF)[197]

The BNF is publication (updated regularly online) prepared by the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain. It provides authoritative guidelines on the use of medicines, and as such it is a central part of any scheme to educate medical professionals in changes related to drug prescribing such as PGx. At present it does not contain much information about the use of PGx in prescribing – perhaps because the evidence base is still developing.

8.4.5.5 Pharmacogenetic exceptionalism?

There is a widely held perception amongst laboratory staff that PGx has more in common with routine biochemical tests or 'point of care' tests than genetic tests in terms of the social and ethical considerations relating to its use – even in cases such as TPMT testing where the mutation is heritable. This may be because there are no known health implications other than therapeutic intolerance for patients homozygous deficient for enzymes like TPMT (Lab 1). It is also rare, but not unheard of, for this information to be required for more than one individual in a given family (Lab 3). Finally it may be that there remains some scepticism about the genotype-phenotype relationship in many of the early PGx exemplars, specifically Cytochrome P450 and APOE-4 (Lab 1, Lab 4). Overall this appears to translate into a general lack of emphasis on the implementation of an informed consent prior to PGx testing. In the cases of cancer patients in particular this is expressed as being of minor importance compared as compared to the patient's overall clinical predicament (as discussed further in the TPMT case study). Previous reports undertaken within the UK have recommended that PGx information should not be considered 'exceptional'.[198]

8.5 Remaining challenges for the regulation of

[196] http://www.nelh.nhs.uk/nsf/inprimarycare/pdf_files/nsf_intro.pdf accessed 23/01/05
[197] http://www.bnf.org/bnf/ accessed 23/01/05
[198] Nuffield Council on Bioethics (2003) *Pharmacogenetics: Ethical issues*, London, Nuffield Council.

pharmacogenetics

It is apparent that at the present time in the UK there are a number of challenges that surround the adoption and satisfactory regulation of pharmacogenetic testing, although in some cases they are applicable beyond the area of PGx.

8.5.1 Development and regulation of PGx products

The full and proper support necessary to generate PGx products and provide PGx testing services consistently and nationally is dependent on compelling clinical evidence. This evidence base, including costs and benefits, remains underdeveloped for the majority of possible areas of potential pharmacogenetic interest. This is likely to be particularly addressed by ongoing work, but is expected to take some time to be resolved. This can only be addressed drug by drug and test by test. Furthermore recent evidence on the incidence and causes of ADRs in the UK suggests that the majority of such incidents are wholly predicable with current pharmacological knowledge being due to, for example, drug-drug interactions.[199] It seems there is a need to disentangle the behavioural causes from the genetic and other environmental causes, and act on each of these rather than focusing solely on PGx if the burden on the NHS of adverse drug reactions is to be reduced significantly.

There are a number of challenges that that arise from the development of PGx products and their reliance on biobanks. These concerns include the addressing of ethical issues surrounding the taking, storage, use and potential re-use of genetic material, particularly in clinical trials.

The approval of PGx products which serve subpopulations rather than being suitable for more wide usage has also been a concern in the UK where there are no formal national incentives for 'orphan' drugs development at present.

Furthermore there are not likely to be commercial incentives or regulatory resources for re-evaluation of approved medicines in the light of emergent PGx data.
Another regulatory challenge that remains to be clearly explored is the question of how a product will be labelled and how enforcement will work in practice if a diagnostic test is required as part of a drug's use. However the organisational challenges of approving a drug and a device together are not in themselves seen by regulators to be an insurmountable problem.

Genetic tests need to be validated for each population, and at present the limitations of PGx diagnostics work in genetically diverse populations are not adequately addressed in the regulatory approval mechanism.

8.5.2 Education

[199] Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A., Walley, T., Farrar, K., Park, B. and Reckenridge, A. (2004) 'Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18820 patients', *British Medical Journal*, Vol. 329, July: 15-19.

To encourage the suitable 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 where these individuals 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, immunohistochemistry may benefit from greater interaction to improve best practice and prevent fragmentation of this emerging field.

8.5.3 Consent

The question of genetic information and the practice of informed consent in regard to PGx testing is an area that needs attention. While practitioners in the field do not appear convinced that PGx testing requires special measures it seems informed consent is not being sought. However this may well be the case with many other forms of testing.

8.5.4 Quality of testing services

Although applicable more generally than just to PGx, the challenge of meeting the cost of providing quality in testing services remains. With the availability of expensive automated systems, best practice and accreditation schemes, it appears lack of resources is likely to become a barrier to quality.

It has been noted previously[200] that tight regulatory controls may make service related innovation more difficult as spare capacity is absorbed by time consuming procedures and increased costs of compliance. Measures need to be undertaken to ensure translatory research can continue at the local level, both to ensure continued innovation in service delivery and to maintain the attractiveness of clinical testing as a career choice for the best and brightest minds.

8.5.5 Expectations

There is a need to manage the expectations surrounding PGx testing in a sustainable manner to ensure continued financial support of research, due to the prolonged period of time it takes for PGx advances to reach the point at which these may be implemented. For example TPMT and cytochrome P450 have been known about for 25 years or more.[201]

8.6 Primary Sources:

[200] Hopkins, M.M. (2004) 'Technique-led technological change and the hidden research system' unpublished DPhil thesis, SPRU, University of Sussex, Brighton.

[201] See Weinshilboum, R. and Wong, L. (2004) 'Pharmacogenomics: From bench to bedside', *Nature Reviews Drug Discovery*, Vol. 3, September, pp. 739-748.

1 Official from the Department of Health
2 Officials from the Medicines and Healthcare products Regulatory Agency
3 Research laboratories
3 Clinical laboratories

Of the laboratories in which interviews were conducted, two are involved in HER-2 testing and three in TPMT testing, one undertakes genetic testing for hereditary diseases only. Three of the laboratories hosted QA schemes.

Chapter 9 Conclusions

Michael M. Hopkins SPRU, University of Sussex

This report has presented detailed case studies of the regulatory context for PGx products and services in the USA, Germany, Ireland, the Netherlands and the UK. It has also described EU level regulation for PGx drug and diagnostic products. A review of industrial views on the US and EU regulatory frameworks is presented in Chapter 4. The definition of regulation used in this report is pragmatic and broad, so as to encompass the multiple levels of factors which may affect the successful use of PGx in healthcare. The key similarities, differences and challenges highlighted by the case studies between regions are summarised here. These findings may provide lessons on how to improve the regulatory context for PGx. However it is important to emphasise that the successful integration of PGx into healthcare systems relies on many of these factors being addressed together as the different parts of the system are heavily dependent on each other:

- The emergence of PGx products will rely on the attractiveness of PGx as an investment area for firms;
- In making PGx investment firms will require clear regulatory frameworks and economic incentives such as drug pricing power, as well as demonstrable demand from clinical users;
- User demand will in part depend on education as well as clinical utility;
- Clinical utility will depend on the availability of timely, accurate and reliable testing services;
- Services will be dependent on the growth of an extensive evidence base, affordable tools and trained personnel.

All of these developments will take time to come together and in the meanwhile will require a nurturing policy environment.

We examine these factors in three sections: The regulation of products, the regulation of services and the wider environment before discussing the remaining challenges.

9.1 Regulation of PGx products

It has been suggested that the potential use of PGx to identify patients who might benefit from a particular drug or reduce the risk to those who might suffer an adverse event will have significant implications for therapeutic licensing agencies.[202] Key areas of include:

[202] Shah, J. (2003) 'Economic and regulatory considerations in pharmacogenomics for drug licensing and health care', *Nature Biotechnology*, Vol. 21, No. 7, pp. 747-753; Webster, A., Martin, P., Lewis, G. and Smart, A. (2004) 'Integrating pharmacogenetics into society: In search of a model', *Nature Reviews Genetics*, Vol. 5, pp. 7-13.

- The gathering of PGx data in clinical trials and subsequent submission for consideration in the approval process
- The licensing of drugs for sub-populations to the exclusion of others
- The approval of a therapeutic in conjunction with a diagnostic device.

The above fall within the remit of drug and device licensing agencies. These developments have further implications for labelling, the use of orphan drug laws and approval of diagnostics. The response to these challenges of the national licensing agencies of the USA, Germany, Ireland, Netherlands and UK as well as that of the EMEA is explored in this section.

9.1.1 PGx capacity building and restructuring at licensing agencies

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 approach to capacity building in the area of PGx is perceived by industry as being robust. Measures taken include the formation of an interdisciplinary pharmacogenomic review group and the undertaking of joint workshops with industry.

In Europe there has been little demand directly from sponsors to the national agencies of Ireland, the Netherlands, UK and Germany in relation to PGx. Indeed it appears that by accident rather than design 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 and so the lack of capability building at national agencies may signal a need to bolster the EMEA's pool of expertise as the importance of PGx rises. At present the EMEA has been able to draw on academics and drug regulators for its PGx related activities.

The EMEA's focus on PGx began in 2000, using workshops to include 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 used in the development of drugs, although the EMEA's licensing remit is not expected to expand to include 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 internally before it can be passed to the assessors as guidance.

Industry opinion (as discussed in Chapter 4) suggests that the FDA approach to PGx is seen as being more pro-active than the EMEA approach.

9.1.2 The 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 the gathering of genetic data, although this is not necessarily for regulatory submission purposes. The FDA responded to the challenge of PGx data use in clinical trials with its voluntary genomic data submission programme and a series of draft guidance documents, culminating in March 2005 with a final release of the pharmacogenetic guidance.[203] An FDA concept paper has also recently been produced on co-development of drug/device products.[204] Given the recent release of both sets of FDA documents it is too early to provide a detailed review of their reception although as reported in Chapter 4, the FDA approach has been broadly welcomed by industry. However challenges remain, notably in 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 firms began to discuss the use of genetic data through one-to-one briefing meetings held 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 view of the EMEA 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 more transparent.

National agencies in the Netherlands and Ireland have not been approached with requests to consider PGx data and at present 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.

9.1.3 The licensing of PGx products

To date there have been no approvals of applications for combined drugs and diagnostic kits in the US or EU. However the licensing of therapeutics in combination with a diagnostic test was seen as presenting significant challenges for the FDA as the boundaries blur 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

[203] http://www.fda.gov/cber/gdlns/pharmdtasub.pdf accessed 01/06/05
[204] http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf accessed 01/06/05

addressed consistency and transparency, and internal communication, in the process, issues which had caused some concerns. Also there are definitional questions with regard to whether PGx-based products will inevitably be defined as 'combination products' under US law. It is expected that the FDA OCP will take on a co-ordinating role with such products, mediating between the different FDA Centers.

Ireland, the UK and the Netherlands already follow a single agency approach with drug and device licensing being undertaken by the same agency while Germany still has separate institutions. Beyond the case studies it appears that Germany's position is the more common as comparatively few countries have followed 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 competency in 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 separate application for diagnostic elements of PGx products made to the national agencies is set to continue, with improved channels of communication between national diagnostic authorities and the EMEA expected to develop 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 not having had any significant experience with PGx products to date. In the UK, Germany and the Netherlands, cases like the approval of the HER-2 kit in conjunction with the centralised EMEA approval of Herceptin are reported to have raised some challenges, but nonetheless were accomplished satisfactorily. However these systems are relatively untested at present as most genomic-based drugs are only now being moved into development. Furthermore there are some concerns as to 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 based only on technical accuracy and not on clinical utility, although apparently this has not raised concerns with the regulators such as the UK's MHRA, as discussed in Chapter 8. Nonetheless this is important as the evidence supporting clinical utility is regarded as one of the main challenges facing PGx, as discussed in section 9.4 of this chapter.

At present the EMEA can only strongly recommend the use of a diagnostic test as part of the labelling process (see below). It is also not clear how enforcement of diagnostic use could be upheld in member states or how non-marketed tests such as those developed in hospital laboratories, and excluded from the IVD directive's scope, 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.

9.1.4 Labelling of new medicines with PGx information and re-labelling of old products to include new PGx information

There are few examples to date of products requiring labelling to accommodate PGx data. When such information about PGx testing is required, there is no standardised manner for this information to be presented on a drug's label or data sheet. As such the inclusion of PGx information in a drug MA is handled on 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 have emerged that suggests a PGx diagnostic would significantly improve the safety of a drug that is already available on the market, there is a legal mechanism (Article 31) that allows for the EMEA to recommend to member states a change of labelling. However this has not yet been applied for PGx. Similarly, the FDA also has the ability of revise drug labelling with the emergence of new data, and has already issued new advice on the basis of PGx data, although mandatory PGx testing has not thus far been retrospectively applied.

In any situation where new data emerge on a licensed drug, regulators have emphasised the need to address scientific uncertainties carefully, and their duty to act only on robust data.

9.1.5 Market segmentation and orphan drug status

Previous reviews of PGx suggest 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.[205] This concern is shared by agencies such as the UK MHRA, which suggests incentives may be needed to facilitate availability of therapeutics for some groups of patients. In the USA, sponsors are provided with 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 such a situation would not be a major challenge. While this system has proved useful for the approval of Gleevec in the USA, Herceptin was not given the same protection.[206] The FDA took the view

[205] Nuffield Council on Bioethics (2003) *Pharmacogenetics: Ethical Issues*, Nuffield Council, London; Shah, J. (2003) 'Economic and regulatory considerations in pharmacogenomics for drug licensing and health care', *Nature Biotechnology* Vol. 21, No. 7: 747-753. Webster A, Martin, P., Lewis, G., and Smart, A (2004) Integrating pharmacogenetics into society: in search of a model, *Nature Reviews Genetics*, 5:663-669.

[206] Shah, J. (2003) 'Economic and regulatory considerations in pharmacogenomics for drug licensing and health care', *Nature Biotechnology* Vol. 21, No. 7: 747-753.

that the patient population for Herceptin comprises people with breast cancer, who number considerably more than 200,000. The FDA was apparently not inclined to define a subset of patients as having a distinct condition based on the genetic characteristics of their tumours. Herceptin was however granted the status of an orphan medicine for the subset of pancreatic cancers that over express HER-2. Medicines are most commonly denied orphan medicine status because of disagreements over how target populations are defined. Although rejections might in many cases 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. The potential need for regulatory agencies to reconsider definitions of orphan medicine in the light of advances in pharmacogenetics was highlighted by numerous respondents to the recent public consultation on the ethics of PGx held by the Nuffield Council on Bioethics.[207]

The Nuffield Council recommended that agencies responsible for the licensing of new medicines pay attention to the possible negative effects of stratification. If pharmacogenetic stratification does provide an economic disincentive for those developing new medicines, consideration should be given to preparing guidance notes that encourage applications to use existing orphan medicine legislation, or any other policy instrument with equivalent effect, to provide incentives for development. The Council further recommended that if orphan medicine legislation is to be applied, consideration is given by the International Conference on Harmonisation to a global approach to orphan medicine legislation. This should include reconsideration of the definition of an orphan medicine, with particular reference to the implications of genetic stratification of both patients and diseases. Orphan drug legislation exists in Germany and the Netherlands, but not the UK or Ireland. European orphan drug provisions remain untested for PGx products.

The EMEA makes the distinction between market segmentation that divides patients according to response, for example due to variations in metabolic activity, and that which divides diseases by aetiology. While licensing of drugs that use the latter category has occurred in the area of cancer drugs, the EMEA has not been faced with an example of the former, and would wish to avoid making such a licensing decision unless this was the only viable option.

9.1.6 Harmonisation

The issue of harmonisation between regulatory 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 opinion in industry is undecided about the time scale over which this might be achieved. Some industry interviewees were sceptical that harmony could be achieved; others were keen that it should be achieved and disappointed with progress to date, while still others felt that harmonisation should not be aimed for too quickly in a field that is changing rapidly to avoid future regulatory changes becoming more difficult.

[207] see http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/page_237.html

9.2 The 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 HER-2 testing with the number of laboratories testing for over expression of HER-2 suggested to be in the hundreds in both the USA and EU. Given the similarity in methods for detection of other cancer related biomarkers it seems that oncology is an area where significant PGx testing will continue to develop. Meanwhile the case studies presented here as well as earlier research[208] suggest testing for CYP450 and TPMT testing have not attracted much clinical interest to date, in part because of the complexity, and time and expense involved in these tests.

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 to be undertaken by pharmacists or physicians, at present this is not evident. The analysis here assumes that such tests will continue to be conducted by laboratory staff in the near term. Laboratories conducting PGx testing are staffed by a range of scientific disciplines such as molecular genetics, clinical chemistry, and histopathology. The scope of tests offered and volume of workload received varies substantially and in some cases research laboratories rather than dedicated clinical laboratories provide services. This causes concern about the adequate provision of services in terms of quality and reliability. The satisfactory implementation of PGx testing services will therefore rely on the prompt uptake of new diagnostic technologies by clinical laboratories for further assessment to reduce the number of such services being provided from research laboratories.

Mechanisms that influence test availability and quality found 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. If the clinical applications of PGx grow substantially in future years, support for these systems will increase and become more important. This has applied to a number of laboratory disciplines in recent years, including testing for genetic diseases.

9.2.1 Licensing of clinical laboratories

The countries studied vary greatly in their use of licensing of 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 UK there are no licensing schemes and, at least in principle, this means that any laboratory can offer the service. None of the countries studied has special licensing for the practice of genetic testing, although a new set of CLIA rules for genetic testing is in development.

[208] Shah, J. (2004) 'Criteria influencing the clinical uptake of pharmacogenomic strategies', *British Medical Joural*, Vol. 328, June, pp. 1482-1486.

9.2.2 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 schemes such as ISO 9001. Laboratory accreditation schemes are established in the USA, Germany, the Netherlands, UK and Ireland. However, smaller countries will often not have 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 USA a proliferation of schemes offers some choice. In the USA the scheme is tailored different disciplines such as molecular genetics, and this approach is also being developed in Germany.

In practice a problem with the accreditation system is that membership of schemes is often not mandatory, or where it is being 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 infrastructural deficiencies that they cannot address because of financial constraints. However the impact on local services of closing these down would be too severe for such action to be considered.

9.2.3 External QA schemes

External QA schemes stimulate the improvement of testing quality by revealing best practice and encouraging its diffusion. As such they are generally positively received by participants. Such schemes identify laboratories that are performing poorly and provide them with assistance. It has previously been noted that QA schemes are not sufficiently developed in the US and EU in the area of genetic testing as a whole.[209] Unsurprisingly there are few dedicated PGx schemes as yet, although HER-2 schemes are well established in the EU and USA, and a global TPMT testing scheme is being piloted by a UK laboratory. This highlights the increasing trend towards international QA schemes. International schemes in particular benefit smaller countries where national 'critical mass' for the launch of a scheme may be lacking. As such the support of international QA schemes could be an important priority for the EU in the field of PGx. It is notable that the existing QA schemes for PGx are not linked to previously established schemes in other areas of genetic testing. The building of such links would be of benefit for cross-fertilisation of ideas and may 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 those in the research base, 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 lack of ability to place sanctions on poor performers frustrates some scheme organisers.

[209] 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.

Some Germany clinical laboratories and UK research laboratories have suggested QA schemes are overly time consuming and so the continued growth of QA schemes may require greater support of some laboratories to enable their participation.

9.2.4 Reimbursement of testing services

Availability of reimbursement for tests can be a crucial driver for the development of diagnostic technologies. For example 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 this is a smooth process. In the USA, PGx laboratories have to undergo time-consuming correspondence with local insurers to receive reimbursement for a new service, although eventually payment is received. In Germany, the reverse operates with reimbursement available for procedures except those explicitly barred from reimbursement by the Gemeinsamer Bundesausschuss. In the UK reimbursement decisions are made at the hospital level, although where there is regional variation, NICE may issue guidance (as occurred in the case of Herceptin and HER-2 testing). In the Netherlands local hospitals also have to make case-by-case decisions. In Ireland most PGx tests are reimbursed without issue due to the small scale of activities at present.

9.2.5 Validation of new PGx tests in clinical laboratories and the use of 'home brews'

Prior to the provision of a PGx test 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 in a technical sense with occurrence of 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.[210] However, as noted in section 9.2 there are no mandatory controls in the EU that influence the introduction of PGx tests into hospital laboratories when those tests are developed in the public sector. Indeed under the EC's IVD directive hospital laboratories have achieved exemptions for conditions that providers in the private sector would be subject to. This has caused some consternation in the diagnostics industry, which suggests that firms will be regulated more heavily if they provide the same services as hospital laboratories. Nonetheless in countries such as the UK where the NHS relies heavily on hospital laboratories, a stricter regime would have significant impacts on the cost of healthcare provision. The situation is slightly different in the USA. Here, non-commercial laboratories are free to develop 'home brew' kits without approval from the FDA. However, to maintain CLIA certification for that service a series of steps must be demonstrated to have been

[210] Shah, J. (2004) 'Criteria influencing the clinical uptake of pharmacogenomic strategies', *British Medical Joural*, Vol. 328, June, pp. 1482-1486.

followed to validate the test prior to its introduction. UK laboratories are also advised under the CPA scheme to validate new services, but in both cases it appears some users feel this process is rather weak.

9.2.6 Ethical concerns and regulatory safeguards

A number of ethical issues surround the practice of PGx testing, notably related to the genetic nature of the information revealed. These issues include protection of patient autonomy, privacy, protection from discrimination, and the retention, storage and retrieval of samples. These issues are explored more extensively elsewhere.[211]

Although not addressed in the above case studies all of the countries studied do have data protection laws that address some of the concerns surrounding patient privacy.[212] On the other hand, informed consent and patient autonomy are not always enshrined in law, but guidelines issued by professional bodies (for example in the USA and Germany) or government ministries (for example the UK's Department of Health) place emphasis on these principles. The application of principles of informed consent remains a challenge in PGx and is discussed further in section 9.4.

9.2.7 Clinical use of PGx information

The effective use of PGx tests in the clinic relies on the take-up of available services by the clinical community and accurate communication of the information supplied.

In the USA, UK, and Ireland the 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 face legal liability in cases where patients did not receive the appropriate advice (for instance if the clinician did not ask that the test be performed), although surprisingly this was not raised as a concern in the US interviews (perhaps because US interviewees did not include physicians).

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 HER-2 have received more attention). However even where guidelines exist, laboratory staff in the UK highlight that compliance is often a problem.
Where tests are requested, communication between laboratory and user can be poor, as highlighted in the German case study. Also, in the UK laboratory staff are 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

[211] Nuffield Council on Bioethics (2003) *Pharmacogenetics: Ethical issues*, Nuffield Council, London; McNally, E., Cambon-Thomsen, A. et al. (2004) '25 Recommendations on the ethical, legal and social implications of genetic testing', report prepared for the European Commission, Brussels.
[212] OECD (2005) *Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Survey of 18 OECD Member Countries*, Paris: OECD.

the implications of test results. However it should be noted that 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 key focus in PGx meetings in the USA according to one interviewee. 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 the education of users is suggested to be difficult in a climate where over-promotion of the laboratory service itself is frowned upon.

The low levels of PGx knowledge that medical professionals currently have remains a significant challenge and is discussed further in section 9.4.

9.3 Wider environment for PGx regulation

In this section we discuss a number of important themes that although not directly linked to the regulation of PGx, are likely to have a significant influence on its application. These include expectations of PGx the impact of PGx, ethical issues surrounding the collection of samples for PGx analysis in clinical trials, and the legal frameworks in place to defend against genetic discrimination.

9.3.1 Expectations surrounding PGx

There is a range of expectations surrounding 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 appear to correspond to the efforts given to its implementation. Of the countries studied, the USA has provided the broadest support for PGx, with enthusiastic policy support, represented by generous NIH funding and well co-ordinated 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 on the assumption that it will have marginal utility rather than being a revolution in medicine. The view at the level of policy in the UK suggests little clinical impact is expected in the short to medium term. In the Netherlands PGx has not been a focus of attention at the policy level although there has been some enthusiasm about the potential impact on therapeutic R&D, but 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 level of policy, and no specific expectations have been reported.

The principal medicine licensing agencies, the EMEA and FDA, have broadly positive views of the technology's prospects. The view of the EMEA expert interviewed (Chapter 3) 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 therapeutic fields more than others. This perception of uneven development appears to agree with observations made by previous commentators.[213] The FDA highlighted the growing role of PGx in drug development especially in sub-populations, although it was more cautious about the prospects for PGx in improving pharmacovigilance given the range of causes linked to adverse events.

In general a reasonable conclusion would seem to be that there continues to be much uncertainly about the impact of PGx, especially as the evidence base remains to be developed in many areas (as discussed in section 9.4.2). At present regulators have only a very limited number of case studies to draw lessons from and the need for and nature of future regulatory change is difficult to anticipate.

9.3.2 The collection of PGx data and samples in clinical trials

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. As discussed in Chapter 4, experience from industry suggests that there is little if any patient resistance associated with the collection of PGx data. However, it has been widely noted that the proliferation of protective measures and the dynamic nature of policies and guidelines at national levels create challenging conditions for firms operating in the EU. Despite their concerns about the challenge of keeping up with regulatory change, firms are keen to co-operate with best practice. As mentioned in Chapter 3, doubts have also been raised about the ability of academic groups to adhere to new requirements associated with the clinical trials directive. Detailed discussion of ethical practice relating to the use of genetic material in research is more fully reviewed elsewhere.[214] The conclusions of these reports remain relevant to future policy in the field of PGx as best practice is still evolving.

9.3.3 Legislation on genetic discrimination

A common concern across countries appears to be that genetic information can be misused in a manner that may prove to be disadvantageous to those tested, whether as part of a clinical trial or in the course of routine medical practice. To this end legislation is in the early stages of preparation in the USA, UK, and Germany. Existing laws in the Netherlands may already grant some protection to patients in the Netherlands. Ireland has no plans for such legislation, but in common with the UK, there is already an

[213] Pirmohamed, M. and Lewis, G. (2004) 'Implications of Pharmacogenetics and pharmacogenomics for drug development and health care', in E. Mossialos, M. Mrazek and T. Walley (eds) *Regulating the Cost and Use of Pharmaceuticals in Europe* (European Observatory on Health Care Systems/WHO Europe), Open University Press, Maidenhead, 279-296..

[214] Nuffield Council on Bioethics (2003) *Pharmacogentics: Ethical Issues*, Nuffield Council, London; EC (2004) 25 Recommendations on the ethical. Legal and social implications of genetic testing. EUR 211120. Luxembourg.

Insurers' Code to prevent the use of genetic information. However, currently it seems that all countries studied still have some way to go in providing comprehensive protection to their citizens – this addresses the field of genetics in general, and PGx would be included under this umbrella in many cases.

9.4 Remaining challenges

At present there are a significant number of challenges that may prevent the widespread development and use of PGx related products and services or result in undesirable consequences. These include a lack of tools, and shortage of evidence necessary to determine clinical utility and cost effectiveness, and hence patient and societal benefits.

9.4.1 Tools for PGx

The platforms to support the routine, reliable and affordable use of PGx are still evolving. Even in the USA where investment in PGx technology has been greatest the current technology is viewed as being too expensive and too slow to merit wide application. Furthermore, technologies such as microarrays generate vast amounts of data that are hugely complex and difficult to analyse, and the technologies are not always robust enough to deliver findings that are reliable. No software to provide sophisticated interpretation of this complex information has yet been developed. Biochemical assays favoured by some US and UK scientists are seen as time consuming and complex.

9.4.2 The evidence base

There is agreement in the findings across the case study countries that the evidence base is underdeveloped for many areas where PGx could be applied. Confirming the clinical validity of genotype-phenotype associations requires detailed research to be undertaken. Furthermore, for a test to be widely used it must perform adequately in the population at large, including ethnic groups, and detect a sufficiently full range of genetic changes occurring in the population. At present the heterogeneity of populations as well as the more complex aetiology of many phenomena such as adverse drug reactions, mean that clinical guidance is not available even for use in tests involving CYP 450 and TPMT where clinically important genotype-phenotype associations have been recognised for many years. There is also a growing acceptance that genetics will not explain the full set of causes of variability in drug response. Some commentators/interviewees 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.

9.4.3 Genetic exceptionalism, informed consent and clinical use of PGx test results

PGx tests, whether based on DNA analysis or other methods, may reveal the presence of genetic changes which have implications for the patient beyond the therapeutic question initially posed. For example, it may reveal information relevant to the patient's treatment with drugs that may be offered in the future, or reveal risk of further diseases or a likely prognosis for an existing condition. It may also reveal information relevant to the medical care of family members.

Furthermore, and in common with other types of clinical diagnostics, PGx test results are not always predictive of the patient's drug response – environmental factors often play a role too – thus a test result cannot be regarded as providing a definitive answer.

A previous study which focused specifically on ethical issues related to PGx concluded that PGx test results do not raise issues unique to those surrounding other forms of diagnostic test.[215] Nonetheless, this is not a universally accepted viewpoint.[216] We therefore cannot exclude the possibilities of specific and novel ethical concerns emerging related to particular PGx tests in the future.

The views from case studies reported here seem to support the conclusion of the Nuffield 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 not clear. 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 it is possible that some PGx tests may need to be accompanied by genetic counselling as is required for some tests for genetic disease, but this will need to be determined on a case-by-case basis.

On the related issue of informed consent and PGx (see the Nuffield Report for a more detailed discussion) the case studies suggest that even basic discussion with patients to elicit informed consent for PGx tests is often lacking, although this is a problem in other areas of diagnostic medicine and not unique to PGx.

[215] Nuffield Council on Bioethics (2003) *Pharmacogenetics: Ethical issues,* Nuffield Council, London.

[216] Pirmohamed, M. and Lewis, G. (2004) 'Implications of pharmacogenetics and pharmacogenomics for drug development and health care', in E. Mossialos, M. Mrazek and T. Walley (eds) *Regulating the Cost and Use of Pharmaceuticals in Europe* (European Observatory on Health Care Systems/WHO Europe), Open University Press, Maidenhead, 279-296.

9.4.4 Promoting quality in PGx testing services

As noted in section 9.2 the PGx testing services supporting clinical practice are supplied by a range of public and private sector laboratories. These laboratories represent a range of scientific disciplines, including molecular genetics, clinical chemistry, and histopathology. The scope of tests offered and the volume of workload vary substantially and in some cases research laboratories rather than dedicated clinical laboratories provide services (see points made above in 9.2.3 and 9.3.4 relating to this issue). Although the case study evidence suggests this is increasingly being discouraged in countries such as the USA and UK, a recent OECD survey[217] notes that progress in genetic testing services has historically been driven by close links between research laboratories and clinical groups. With many services only available from research laboratories a balance is needed between effective regulation and encouragement of innovation.

This diversity of laboratories brings a diversity of approaches for 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 are yet to emerge, and those that are active are not associated with 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. Indeed in some cases such as HER-2 testing it is possible that different methodologies may be promoted by different communities and cross-disciplinary initiatives are needed to bring key individuals together to inform best practice.

One approach that is often associated with standardisation is the availability of a commercial kit. However, in practice, including the example of commercial tests for HER-2 testing, 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 those developed within testing laboratories (so called 'home brews'). However the cost differential between the price laboratories must pay for these kits and the price they can pay for the constituent elements provides a strong incentive for laboratories to find ways of manufacturing their own kits or modifying existing ones. The cost of commercial kits has been cited as a specific factor preventing standardisation in the UK, USA and Germany.

[217] OECD (2005) *Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Survey of 18 OECD Member Countries*, Paris: OECD.

9.4.5 Education of medical professionals

The need for increased education in PGx for medical professionals is widely recognised. However, this is seen as being 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 so even at the leading US centres as little as 90 minutes is given over to such training. The UK case study revealed that it is not just specialist physicians that require training but also nurses and junior doctors, as they too are often required to follow PGx protocols. The need for further training is acknowledged in the German and Irish studies also, although in the case of the former it was noted that physicians already have too much new information to absorb.

The UK case study reveals that education in itself is also not necessarily sufficient to guarantee the uptake of PGx, as the perceived relevance of tests varies between specialisms according to the frequency with which clinicians use particular drugs and are exposed to incidences of adverse events. In Germany PGx is not seen as relevant by some physicians who see the complexity of phenotypic and genotypic interaction to be accurately predicted by a single testing methodology.

9.4.6 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. Indeed 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 some evidence that these are also responsible for the vast majority of ADRs. The FDA has demonstrated a willingness 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 where this is deemed appropriate. Where older drugs generate little revenue for firms it is not likely that these firms will sponsor the necessary regulatory process to reappraise these drugs in the light of PGx data. Although governments in the Netherlands and UK have funded some research on PGx and licensed medicines, it seems that at the present time 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 can make the most use of PGx in widely used off-patent medicines.

Furthermore there is a need for incentives to be created to make re-licensing economically feasible, although it is not clear how a single firm would benefit in commercial terms from linking a diagnostic test to a drug if multiple generic producers existed in a market place already.

9.4.7 Intellectual property rights

In the USA there has been at least one case of a PGx test, a molecular genetic testing service for TPMT, being withdrawn by a hospital laboratory following enforcement of patent rights by the assignee firm (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 uniformly problematic 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 noted in Ireland, and in the Netherlands the issue seems to be whether hospitals that have developed a test should themselves be focusing on exploiting such research through patenting.

9.4.8 Further potential challenges

A number of challenges were indentified in individual countries that may also be applicable in other regions, but have not been widely discussed in the case studies as a group. These included:

- consumer confidence in the industry particularly where the handling of genetic information is concerned;
- ensuring the availability of data on different patient populations to undertake drug efficacy and safety studies as well as the harmonisation of ethical committee standards that oversee these processes (for example such as those surrounding the collection and retention of biological samples from patients in trials).

Interestingly some potential challenges raised in recent publications were not raised by our sources during the course of this study. These include:

- The ethical challenges presented by racially bounded prescribing patterns.

The heart-failure drug BiDil has recently been approved by the FDA only for use in African American patients. In lieu of a precise genotypic factor that separates responders from non-responders, race appears to have been used as a proxy. Perhaps one reason for the lack of emphasis this received from sources used in this report is that race is already acknowledged to be a poor category and is not anticipated to be used widely by regulators.[218]

- Disproportionate barriers for academic PGx research.

A number of factors may conspire to make academic research in PGx more difficult than commercial research. Academics wishing to undertake genetic association studies with new drugs may face industrial reticence over collaboration if industry believes it may be obliged to share the results of such research with regulators. Furthermore researchers report a mounting bureaucratic burden associated with clinical trials undertaken in the EU, as well as increasing difficulty in meeting ethical and regulatory

[218] Stacy Lawrence 2004, 'First ethnic drug', *Nature Biotechnology*, Vol 22, No.9 September, p.1066; Rahemtulla, T. and Bhopal, R. (2005) 'Pharmacogenetics and ethnically targeted therapies', *British Medical Journal* Vol. 330, May, pp. 1036-1037.

requirements.[219] With less resources than firms, these demands place a disproportionate burden on not for profit organisations. The extent to which these factors affect academic research have not been assessed in this report (Part 3), although Part 1 of this ESTO study does focus in more detail on the wider research environment for PGx.

[219] Tucker, G. (2004) 'Pharmacogenetics – expectations and reality', *British Medical Journal*, Vol. 329, July, pp. 4-5.