

Regulating pharmacogenomics

An overview of developments in various countries and industry response to regulatory initiatives

A report for Health Canada

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Foreword

This report has been prepared for Health Canada to inform ongoing work that the Canadian government is undertaking in the area of genomics and pharmacogenomics, by expanding knowledge of how regulators in other countries are adapting traditional models and requirements in the light of the advances in pharmacogenomic research, specifically:

- the use of pharmacogenomics in drug development
- the issues around biomarker validation
- development of new clinical trial design models
- the co-development of drugs and pharmacogenomic tests
- the use of in-house developed pharmacogenomic tests

The study examines the pros and cons of the different models and regulatory requirements as regulators seek to balance the need to foster the timely adoption of useful new healthcare technologies and the need to ensure patient safety through proper evaluation.

This report outlines the scope and content of such initiatives, explores the experience of regulators and other stakeholders to date, and identifies likely future trends and lessons learned in other regulatory jurisdictions that may be useful for the Canadian context.

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Key terms

ACCE – framework for evaluation of a test, this encompasses four criteria:

Analytic validity refers to the accuracy with which a particular genetic characteristic (for example, a DNA sequence variant) can be identified in a given laboratory test

Clinical validity describes the accuracy with which a test predicts a particular clinical outcome; when a test is used diagnostically, clinical validity measures the association of the test with the disorder; when used predictively it measures the probability that a positive test will result in the appearance of the disorder within a stated time period

Clinical utility is the likelihood that using the test result will lead to an improved health outcome; to evaluate this, the important information is about the effectiveness of the interventions available for people who test positive and the consequences for people with false positive or false negative results

Ethical, legal, and social implications: evaluation of these is essential in establishing the full impact of testing

Biomarker - a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

In-house test – test developed for in-house use by a clinical laboratory (i.e. the test is not then sold/distributed to other labs).

Pharmacogenetics - the study of inter-individual genetic variation to drug response.

Pharmacogenomics – the application of genomics to the study of human variability in drug response. Thus pharmacogenomics is an umbrella term which encompasses both the heritable biomarkers studied in pharmacogenetics and other genomic biomarkers such as proteins and enzymes. (Some use the term pharmacogenetics more to refer to the application in clinical practice and pharmacogenomics to the application in drug discovery, we have not used this definition).

Acronyms

BIO Biotechnology Industry Organisation

CLIA(C) Clinical Laboratory Improvements Amendments Committee

EMA European Medicines Evaluation Agency

FDA Food and Drug Administration

ICH International Conference on Harmonisation

IPRG Interdisciplinary Pharmacogenomics Review Group

IVD in vitro Diagnostic

NATA National Association of Testing Authorities

NCI National Cancer Institute

NIH National Institutes of Health

NPAAC National Pathology Accreditation Advisory Council

OCPB Office of Clinical Pharmacology and Biopharmaceuticals

OIVD Office of In Vitro Diagnostics (FDA)

PDMA Pharmaceutical and Medical Devices Agency

PhRMA Pharmaceutical Research and Manufacturers of America

SACGHS Secretary's Advisory Committee on Genetics, Health and Society

SACGT Secretary's Advisory Committee on Genetic Testing

VGDS Voluntary Genomic Data Submissions

I Introduction

The promise of pharmacogenomics is that it will solve two major problems in healthcare – the diminishing productivity of the drug development process and the unacceptably high proportion of patients who receive either no benefits from drugs or experience adverse events. Its proponents suggest that pharmacogenomics will be part of a fundamental transformation in the drug discovery and development process, where currently clinical trials are designed to observe effects in populations rather than to give information on inter-individual variation in drug response. Whilst trial enrichment and population stratification are not novel, the promise of genomic biomarkers is that they will encourage the widespread systematic use of such techniques. This report will look at the regulation of pharmacogenomics in two areas: the drug discovery and development process and clinical practice.

Drug discovery and development

There are three broad approaches to the use of pharmacogenomics in drug discovery and development:

- Target elimination - screening out those drugs where pharmacogenomic factors have negative impact on safety or efficacy
- Target identification - using pharmacogenomic markers as targets for drugs
- Refine understanding of safety and efficacy through analysis of pharmacogenomic response and where appropriate build that data into labels and clinical practice

P450

A significant proportion of drugs are metabolized by the action of cytochrome P450 enzymes which act in the liver to break down a variety of chemicals. Depending on the P450 polymorphism carried then patients may be poor metabolisers, resulting in reduced drug effectiveness, or rapid metabolisers who fail to achieve therapeutic plasma levels at ordinary doses. The drug industry has tended to drop drug candidates that are primarily selective substrates for these polymorphisms.

Clinical practice

Genetic testing of individual patients can be used to guide drug treatment choices in three ways

- to adjust doses
- to choose the most effective drug for a particular individual
- to avoid serious adverse events

Herceptin

Herceptin is a cancer drug which targets the tumour growth factor receptor, HER2/neu. A subpopulation of breast cancer patients have tumours where the receptors are present in large numbers. Herceptin blocks the action of the receptor and kills the cancer cells that carry it, slowing the growth of tumours. Since the treatment is directed specifically at the receptor, it only helps those women who have the relevant tumour profile. Thus treatment selection is based on a diagnostic test to identify those women who are HER2/neu positive.

Caution about progress

Although the field has seen some early and notable successes such as Herceptin, the impact of pharmacogenomics nevertheless been limited thus far. The Royal Society issued a cautious view of the likely timescale in a 2005 report :

- Currently, pharmacogenetics has very little impact on clinical practice;
- Pharmacogenetics is unlikely to revolutionise or personalise medical practice in the immediate future;
- Industry will continue to favour drug candidates that avoid the effect of genetic variation.¹

Yet pharmacogenomics enthusiasts continue to be bullish, last month Allan Roses of GlaxoSmithKline spoke to an international gathering saying he wanted to “attack the notion that personalized medicine and pharmacogenomics are years away.” He presented a number of promising new developments in GSK’s pipeline including Tykerb, a breast cancer drug, an obesity drug and a diabetes drug with potential for use in the treatment of Alzheimer’s Disease.

There is now a general consensus that progress will be much slower than was first hoped by many and much activity is now focused on understanding why this is and what can be done about it. Some of the problems relate to economic incentives and disincentives for the adoption of new approaches to product development, some relate to structural issues that inhibit the adoption of new technologies, some relate to the complexity of the science. Regulatory agencies such as FDA and EMEA who hold out much promise for the field are amongst those trying to address these issues.

Given their responsibility for the development and enforcement of standards for drugs and devices, regulatory agencies are uniquely positioned to shift the pharmaceutical industry from its preferred block-buster drug model aimed at broad populations to one which is more targeted, and to facilitate the participation of diagnostics companies in this goal.

Pharmacogenomics, although an exemplar for novel approaches to drug development, is but one aspect of a more general trend – the FDA’s Critical Path initiative and EMEA’s Roadmap both position pharmacogenomics at the heart of a broader agenda for the enhanced use of novel biomarkers in drug development, diagnosis and screening, and the review of existing clinical trial design and statistical tools for drug evaluation. This agenda represents a shift in the role of regulatory agencies, from the guardians of public safety to a wider public health mission as supporters of the project of translational medicine.

Tykerb

Like Herceptin, Tykerb targets women whose tumours overexpress the Her2/neu protein, but the new drug also targets EFGR. As well as having a pharmacogenomic target population the new drug’s Phase III trials have benefited from analysis of a small number of adverse events (mainly diarrhea and skin rash but some more serious) which have been correlated with CYP2C19 alleles (genes with a well-established role in drug metabolism).

¹ Royal Society *Personalised medicines: hopes and realities* (London, 2005)

At the heart of the approach taken by FDA and EMEA is what we might call the two-pipeline problem. The first pipeline problem is in drug discovery and development and biomarkers are seen as the solution; the second pipeline problem is in the discovery and development of biomarkers.

The translation of pharmacogenomics into clinical practice has generally been slow. Lack of clarity on the regulatory response to pharmacogenomic data has been cited as a factor which may be delaying the development of new pharmacogenomic products. Whilst it promises much, pharmacogenomics raises fundamental questions for the regulation of drugs and devices:

- Complexity of the science e.g. microarray data
- Lack of standards and processes for biomarker validation
- Challenge of co-developed drug/device technologies
- Clinical trial design
- Re-labelling of existing drugs with well-established pharmacogenomic variants
- Role of post-marketing surveillance and Phase IV studies
- Different regulatory regimes for manufactured devices and tests developed in-house

Pharmacogenomics raises significant regulatory challenges for the diagnostics arm of regulatory agencies. Firstly, there is the technical complexity of the tests and the need for standardization of platform technologies such as microarrays, and then there is the challenge of validating the results of tests that may analyse a vast number of biomarkers simultaneously. Added to these technical challenges is the heightened importance of pharmacogenomic tests, given their likely direct impact on the treatment of patients. But if pharmacogenomics raises the stakes for diagnostics regulators - because test results will have a more direct impact on patient care - it also presents new challenges for drug regulators who are less familiar with the diagnostics sector and the challenges of biomarker validation and test evaluation. New developments will bring fresh regulatory challenges, for instance, the advent of point-of-care pharmacogenetic testing will raise significant evaluation issues given the complexity of interpretation of even well-established markers such as the CYP450 genes.²

Although the adoption of pharmacogenomics in the drug development process has been gradual, it is now affecting every stage – from Phase I to Phase IV (with most activity in phase I/II). It is a two-way process with regulators having to adjust their systems to take into account the new technologies being adopted by industry and with the regulatory agencies influencing the adoption of pharmacogenomics through the development of new guidance documents.

In general, regulatory authorities are moving cautiously, seeking to ensure that they do not act prematurely in a fast-developing area of science. However, general trends are identifiable including the establishment of new mechanisms for voluntary sharing of genomic data outside the formal approval process; the development of guidance on regulatory processes and types of data needed, and moves towards international co-operation and harmonisation

² Japan jumps towards personalised medicine *Nature* 2005 Oct 6;437(7060):796.

Before outlining these and other initiatives, it may be useful to clarify what we mean by regulation. Although this report is focused on the activities of regulatory agencies like FDA who have responsibility for approval of new drugs and/or devices, they are not the only gatekeepers with a role in ensuring the quality of new healthcare products. A broader definition of regulation would view oversight as operating at three levels: statutory controls, resource allocation and clinical governance.³ So, for instance, the use of a pharmacogenomic test might be regulated at the first level by standards set by a statutory licensing body; at the second level by the requirements established by the reimbursers (often through health technology assessment); and, at the third level by the rules and guidelines set by professional bodies, healthcare organisations and other groups, which control the practice of medicine.⁴ Whilst this report focuses on activities at the first level of regulation, the other two levels of regulation are important in considering the overall strategy adopted to minimise risks and maximise the benefits of pharmacogenomics.

Finally, in analysing the regulatory activities we have set out here it may be helpful to think of the practice of regulation as encompassing three broad areas of activity: information-gathering; standard setting and behaviour modification.⁵

In general regulatory agencies see pharmacogenomics as a promising opportunity to improve the safety and efficacy of medicines. But as an emerging area of clinical science they recognise that it will require regulatory flexibility and a willingness to engage with industry.

There can be no doubt that the FDA is leading the way, in part because it simply has far greater resources, in part because the Agency has prominent champions of pharmacogenomics in its leadership. The work of the FDA in this area is marked by a high level of engagement with industry. The EMEA is also very active, albeit at a slower speed and smaller scale, reflecting both the resources available and the complex political relationship between EMEA and European member states. Japan has also begun to take action in this area, as has Canada.

A number of general trends are identifiable:

- Issuing of guidance on regulatory processes and data requirements
- Development of mechanisms for sharing genomic data outside the regulatory process
- Organisational restructuring to meet new challenges
- Gradual accretion of experience (for regulators and industry) through approval of new products and/or re-labelling of existing ones
- Moves towards international co-operation/harmonisation

Although much emphasis is placed on the potential of pharmacogenomics, regulators do not espouse a 'genetic exceptionalist' viewpoint. Both FDA officials and EMEA committee

³ Burke W. and Zimmern R.L. (2004) 'Ensuring the appropriate use of genetic tests' *Nat Rev Genet.* Dec; 5 (12):955-9

⁴ Regulatory pressure can also be applied through consumer law and private law remedies to compensate patients who suffer avoidable harm.

⁵ Hood, C et al *The government of risk – understanding risk regulation regimes* (Oxford, 2001) pp24-7

members recently expressed the view that pharmacogenomics, unlike other forms of genetic testing, does not present any special ethical or social concerns.⁶

One general regulatory trend worthy of note is the merger of drugs and device regulatory agencies which has occurred in the UK, Japan and Switzerland. This trend is one which should help to address the organisational challenges presented by the regulation of pharmacogenomics, for instance in the area of co-development of a drug and device. However, it should be noted that EMEA, the pan-European regulatory agency for drugs and a European champion for pharmacogenomics, currently has no authority over devices, despite its leading role within Europe in the regulation of pharmacogenomics.

Regulatory agencies are keen to achieve a harmonised approach to this area and have made some progress in this regard. Leading ICH regulatory authorities such as FDA, EMEA and PDMA are not only recommending the use of pharmacogenomics in drug development but beginning to explore how they can forge a common approach. The development of transnational policies and regulatory standards and processes may assist regulators in guiding and promoting the adoption of pharmacogenomics.

We shall outline regulators' activities through an analysis of three areas: their efforts to prepare themselves for pharmacogenomics (both through internal reorganisation and familiarising themselves with genomic data); activities relating to drug discovery and development and finally pharmacogenomics in clinical practice. We shall then analyse industry responses to these regulatory activities.

⁶ Felix Frueh, FDA and Eric Abadie, EMEA/Affsaps at DIA Paris meeting, February 2006

2 A learning process – getting ready for pharmacogenomics

Overview of individual agencies

FDA's Critical Path

The FDA's enthusiasm for pharmacogenomics has been fostered by a number of senior figures including Deputy Commissioner Janet Woodcock and Larry Lesko, Director of the Office of Clinical Pharmacology and Biopharmaceuticals (OCPB). Dr Andrew von Eschenbach, Acting Commissioner, is a well-known proponent of pharmacogenomics and, assuming his appointment is confirmed, he can be expected to act as a powerful champion for pharmacogenomics with the Agency (in his previous role as head of the NCI he worked with the FDA on a programme to streamline the development of cancer drugs, which included as one of its central goals the development of novel biomarkers for use in drug evaluation).⁷

The development of the FDA's regulatory approach, has been an iterative process involving regular consultation with industry, often through workshops organised in collaboration with trade bodies such as PhRMA and BIO. For instance, the development of a process for sharing genomic data on a voluntary basis was first discussed at a public workshop in 2002, leading to draft guidance in 2003, and then an extensive period of consultation culminating in a final guidance document in 2005.

FDA activities include:

- Formal guidance documents
- External activities including development of consortia for biomarker development
- Cooperation with regulatory agencies in other countries
- Internal activities including
 - Reorganisation
 - Education and training
- Industry and stakeholder consultation/education through
 - workshops and other public meetings
 - articles in scientific journals
- Regulatory decisions
 - New approvals for drugs and devices (individually or co-developed)
 - Relabelling of existing drugs (sometimes in co-approval with new tests)

As was noted earlier, regulatory activities around pharmacogenomics have been motivated by a concern about the slowdown in the drug pipeline and realization that a number of new technologies might be able to both improve the success of drug development and improve safety and efficacy. The FDA's thinking on these issues was given official expression in the Critical Path report published in 2004, which identified biomarkers as having great potential

⁷ FDA spades field for personalized medicine, *Biotechnology Healthcare*, February 2006

to increase the productivity and success of drug development and pharmacogenomics as a particularly rich source of new biomarkers.

The emerging techniques of pharmacogenomics and proteomics show great promise for contributing biomarkers to target responders, monitoring clinical response, and biomarker targets of drug effectiveness. However, much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used. Specific, targeted efforts could yield early results.⁸

FDA Critical Path report 2004

The FDA has finally received funding for the Critical Path initiative and has published an Opportunities List which details priority work areas. The accompanying report again places an emphasis on the role of genomic biomarkers in the development of personalised medicine and the Opportunities List identifies a number of potential projects: including genomic safety markers for predictive toxicology and the need for new collaborative efforts in the area of biomarker development.⁹ These will be explored further in the section on biomarker validation.

EMA's Road Map

The EMA has been developing its work on pharmacogenomics since at least 2000 when it identified a series of priority activities for this area. In 2002 it became the first regulatory agency to establish a dedicated pharmacogenomics expert group and its working paper on terminology was also a groundbreaking initiative.

The EMA's Road Map report is the institution's strategic plan for the next ten years. As such it has a wider focus than the FDA's Critical Path paper, encompassing major political developments such as the inclusion of new EU member states in the EMA umbrella and the changing relationship between EMA and the regulatory agencies in individual states. Like the Critical Path paper, the EMA Road Map report highlights the regulator's twin goals of ensuring public safety and facilitating the rapid transfer of innovative new medicines into healthcare, but the Agency's report also stresses its role in economic development and responsibility to support the European pharmaceutical industry. However, both reports share a common concern with the pipeline problem.

⁸ Critical Path White Paper, FDA 2004

⁹ Critical Path Report and Opportunity List, FDA 2006

Independent research has revealed that one of the contributing factors to the fall in innovative productivity lies in bottlenecks during the development of innovative medicines. Therefore, initiatives should focus on addressing the encountered difficulties in the development stage by exploring innovative approaches in drug development. This should facilitate the process between basic research and the development of a commercial product.

EMA Road Map 2005

Thus, like the Critical Path initiative, the EMA's Road Map expresses concern about the bottlenecks in drug development and suggests that the solution is research and innovation to create a "product development toolkit", (a phrase also used in the Critical Path report) and a greater emphasis on translational research. It commits the EMA to developing a strategic plan for new technologies, but whilst the Road Map does identify pharmacogenomics as one of an important group of new technologies, it does not explicitly suggest that it is part of the solution to the decline in pharma productivity.

Support for pharmacogenomics, along with other emerging technologies such as gene therapy and tissue engineering, will be provided through a number of mechanisms, including:

- establishment of an Innovation Task Force
- creation of forums for early dialogue with sponsors of new technologies
- networking to draw on expertise in academia, industry and learned societies
- development of new guidelines

The Road Map highlights a number of other priority areas relevant to this report:

- early engagement with sponsors as part of an ongoing dialogue of scientific and regulatory advice for new submissions
- collaborative work with its international peers, both through ICH and through bilateral relations with FDA and other agencies
- a greater emphasis on post-authorisation activities including conditional approval and pharmacovigilance.

EMA activities include

- Formal guidance documents
- Cooperation with regulatory agencies in other countries
- Internal activities including
 - Reorganisation
- Industry and stakeholder consultation through
 - public meetings
- Regulatory decisions

Organisational changes

One of the clearest signs that regulators are adapting their working practices to pharmacogenomics is the establishment of new groups to deal with both the scientific review of data and the development of policy.

a) FDA

The Interdisciplinary Pharmacogenomics Review Group (IPRG) brings together staff from the devices and drugs sections of the FDA with the aim of creating a scientific and regulatory framework for reviewing genomic data. It is the primary review body for Voluntary Genomic Data Submissions (VGDS) but it can also play a role in the review of formal product submissions (although these will be handled primarily by the relevant review division/s). Its membership includes senior FDA officials such as Janet Woodcock, Larry Lesko and Steve Gutman (Director of the Office of In Vitro Diagnostics (OIVD)) and it is chaired by Felix Frueh, Associate Director for Genomics in the OCPB.

The IPRG brings together the disparate pharmacogenomics expertise of all the relevant FDA Centers and seeks to influence both the FDA's internal approach to pharmacogenomics (for instance, by harmonising review practices across the Centers and developing educational resources for FDA staff) and the external environment (by engaging with industry in public consultations and with other regulatory agencies internationally e.g. joint activities with EMEA). By including a mixture of policy-making officials and scientific reviewers the IPRG influences both the daily practice of regulation by FDA and the strategic development of the Agency's work around pharmacogenomics.

Whilst the IPRG brings the whole agency together, reorganisation has also taken place within individual divisions. On the drugs side, there is the Pharmacogenomics Working Group which is located in the OCPB, and works with the IPRG on the activities outlined above. On the diagnostics side, OIVD has established a new inter-disciplinary working group to establish common standards and mechanisms for review of new biomarkers in the fields of in molecular diagnostics, genomics, proteomics and multiplex technologies, and it has used its new user-fee income stream to recruit over six new staff with expertise in these areas to ensure rapid and appropriate review of these new technologies. Between the drugs and devices divisions, sits the Office of Combination Products (OCP) led by Mark Kramer, which has a role as an intermediary brokering the involvement of different divisions when a company needs to speak to more than one arm of the FDA for a formal submission.

b) EMEA

The Innovation Task Force (ITF) has a broad role within the EMEA to co-ordinate scientific and regulatory expertise in the field of emerging therapies and technologies including gene therapy, stem cell therapy and pharmacogenomics. The ITF has an external role in the development of policy in this area, so ITF staff members liaise with colleagues within the EC and individual member states; develop relationships with other regulatory agencies such as FDA; and participate in policy-making forums such as the OECD. Within ITF, the work on this area is led by Dr. Marisa Papaluca-Amati.

The Pharmacogenomics Working Party (PGWP) performs a similar role to the ITF but at Committee level, bringing together expertise from across EMEA and its network of scientific

reviewers. It performs the same function as the FDA's IPRG as the body which reviews genomics data submissions through the EMEA's system of briefings meetings. The PGWP is made up of an equal number of regulatory scientists and academic scientists with experts in the evaluation of medicine and devices.

c) Japan

The Pharmacogenomics Discussion Group (PDG) brings together 16 members of PDMA from the different review divisions (new drugs, safety and devices) with the goal of exchanging and sharing data, maintaining consistency in consultations and promoting appropriate clinical trials using pharmacogenomics.

Information gathering - voluntary submissions

Regulators' initial engagement with pharmacogenomics has been primarily focused on information-gathering. As a key part of that activity, regulators have been encouraging companies to share their pharmacogenomic data in voluntary processes outside the formal regulatory mechanism.

These initiatives began around five years ago when it was clear that the pharmaceutical industries were making use of pharmacogenomic data in the drug development process, but this activity was not apparent in the formal drug submissions seen by regulatory agencies. Anticipating a growing role for pharmacogenomic data in drug development, and wanting to foster this development, the FDA and other agencies instituted mechanisms for the submission of genomic data outside the formal regulatory approval process in order to:

- Learn more about how industry is using pharmacogenomic data
- Prepare regulators for its inclusion in the regulatory system by developing their scientific understanding of its application by industry in research and development, allowing for the development of both appropriate technical expertise and the generation of sound policy
- Encourage use of pharmacogenomics by allowing industry to explore its use with regulators without prejudicing drug submissions

The expectation was that regulators should become more familiar with pharmacogenomic data and that industry should become more comfortable with sharing such data with regulators so that formal pharmacogenomic submissions would be dealt with more easily and without unnecessary delays. The process also gives industry participants an opportunity to influence regulators' approach to pharmacogenomics as reflected in guidance documents and standards.

Having learnt from such activities this voluntary approach has now been supplemented by guidance on how to use pharmacogenomic data in formal submissions.

a) FDA – Voluntary Genomic Data Submissions

FDA first proposed the idea of voluntary submissions at a public workshop in May 2002 using the concept of a 'safe harbor'. After this initial consultation with industry the Agency formally initiated the programme with draft guidance on pharmacogenomic data submissions in November 2003. Following extensive consultation and feedback from stakeholders a final guidance was issued in March 2005. The guidance covers both formal regulatory submissions and voluntary ones, although its main emphasis is on the latter (termed voluntary genomic data submissions, or VGDS). Formal submission requirements will be considered in the section on drug discovery and development.

The significance of this innovation lies in the fact that this is the first time that industry has been invited to share exploratory data on a voluntary basis outside the formal approval system. It reflects a far broader culture change within FDA, in which the Agency interacts with the industry in a more open, informal and receptive manner as it seeks to develop its role as a promoter of safe and effective new medical technologies.

VGDS can be used at any point in the drug development process to review new exploratory data that may help to identify and validate novel biomarkers. The submissions are free, both in the sense that there is no fee from FDA and that data is viewed without prejudice to subsequent formal submissions. The 'without prejudice' nature of the process works both ways – a VGDS submission does not act as a formal pre-submission review process, for instance, companies are advised not to request agreement on clinical protocols or studies for approval of an application as part of a VGDS. Feedback received from the IPRG does not affect the independent review of a related formal submission by the staff in the relevant review division and, to ensure this separation, staff who review a VGDS do not take part in any associated formal submissions. Nevertheless, the process allows both companies and the FDA to prepare themselves for regulatory submissions.

As well as introducing and encouraging the use of the new voluntary submission pathway, the guidance on pharmacogenomics data submissions explains the types of data that can be submitted and how the Agency will handle the submissions; it sets out the role of the IPRG and it introduces a classification of genomic biomarkers:

However, the guidance does not offer direction on:

- how to validate genomic biomarkers
- the application of genomic biomarkers
- the emerging fields of proteomics or metabolomics

The FDA received the first VGDS submission in March 2004 and two years later there have now been 25 submissions and 15 sponsor meetings held; two of these have been bilateral meetings with EMEA. The submissions cover a broad range of therapeutic areas including cancer, obesity, depression and Alzheimer's Disease. The scientific scope of the submissions is equally wide-ranging including biomarkers, genotyping devices, microarrays, biostatistics and enrichment design.¹⁰

¹⁰ Figures provided by Felix Frueh, FDA in presentation at DIA Europe meeting March 2006 – Co-development of drug and test – is it a special challenge with PGx?

We have an evaluation of pretty complex raw data, such as microarray data, that we are engaging in, and the dialogue along with that evaluation has been critical to understand and learn what they are doing ... This is a fairly broad, fairly comprehensive discussion, and it covers a lot of areas. It's actually changing the way the FDA looks at how we do things.¹¹

The FDA clearly views the process as a success, citing the range of submissions they have received, the fact that some sponsors have made more than one submission or have followed up an initial submission with a second one on the same area, and the results of a formal survey which showed general sponsor satisfaction with the VGDS process.

The VGDS submissions have provided FDA with really a wealth of significant genomic data and information on numerous therapeutic, scientific, and technical areas which would otherwise be unavailable. So in that sense, the guidance really was successful.¹²

Given that the focus of the guidance document is clearly on the use of genomic data in drug approval, there is some ambiguity about whether device manufacturers are being encouraged to share their exploratory data through VGDS. Although FDA state that it is for both sectors, and they have received two submissions from device companies, at least one leading device manufacturer takes the view that the VGDS is “just for pharma”.

However, for device companies there is an alternative to the VGDS which is a pre-IDE (Investigational Device Exemption). It has the same general benefits as the VGDS in that there is no user fee and it is without prejudice to formal submissions. It gives access to current FDA thinking without binding the sponsor or FDA and gives an opportunity to gain agreement on the criteria and data needed to demonstrate the safety and effectiveness of a device prior to clinical trials commencing. However, this process is about protocol design rather than the review of exploratory data.

b) EMEA – Briefing meetings

The EMEA has instituted a similar process to the FDA’s VGDS arrangements: pharmacogenomics briefing meetings. A concept paper setting out the purpose and scope of the initiative was published in 2003 and a formal draft guideline was issued for public consultation in March 2005, a final guideline should be published in 2006.

Briefing meetings review scientific data but also consider the jurisdictional and regulatory aspects of the submission as appropriate. Fourteen briefing meetings have been held to date,

¹¹ Felix Frueh, FDA speaking at SACGHS, June 2005

¹² Allan Rudman, FDA speaking at SACGHS, October 2005

involving submissions across a range of therapeutic areas including diabetes, cancer and depression. The guidance on the briefings indicates the format of meetings, the format for submissions and the types of data which they expect to see.

Compared with the FDA process the EMEA system has less of a clear delineation between the voluntary submission and any ensuing formal submission, since PGWP members who participate in briefings meetings are also likely to be involved in any subsequent evaluation for approval. EMEA see this as an important aspect of the educational process for review staff.

c) Japan

The PMDA, the Japanese regulatory authority, has also published guidance on the use of pharmacogenomics data in regulatory submissions. Draft guidance was issued in 2004 for public consultation and final notification was issued in March 2005. This guidance asked pharmaceutical companies to provide details of their past, current and planned use of pharmacogenomics in clinical trials including data such as the target disease for treatment, genes under investigation, sample size and trial objectives with a deadline for submission of September 2005. So unlike the EMEA and FDA processes, what is being sought at least initially is some very general details about the type and scope of studies being conducted rather than detailed scientific data from individual trials or projects.

As with the FDA and EMEA systems, all data provided under this process is confidential, and will not be used for regulatory decision-making (although manufacturers are told that if they have data that impacts on the indications for use, dosage guidelines or safety then that data should be part of any formal submission). The precise intentions of PDMA, for instance how they will act on the data they receive, was not clear initially; indeed there was some concern amongst pharma companies that the provision of data was mandatory, although it was subsequently clarified that this was indeed a voluntary process and that the intention was to develop PMDA's experience with pharmacogenomics in preparation for development of a fuller guidance.

d) Bilateral meetings

EMEA has held two joint briefings with FDA. The first was held in May 2005 and a further four sessions are planned in 2006. Both agencies report that this is a successful initiative so far. The review formats and processes differ between agencies but the bilateral meetings have shown that their approach to the science is consistent. This is part of a wider process of collaboration in which the agencies are sharing information on everything from new drug applications submitted to safety information. They are also conducting a benchmarking exercise in which conflicting decisions about a single drug are jointly analysed to understand the differences in criteria.

Analysis

In a situation where industry wants clearer guidelines but fears the premature imposition of inappropriate or unduly burdensome regulation, the systems for voluntary genomic data submissions in Europe and the US represent an important first step in ensuring that regulators act on the basis of a clear understanding of the science of pharmacogenomics and its application to drug development.

The guidelines on the format and content of data submissions is perhaps a useful early indication to pharmaceutical companies of the standards which may be applied in the context of statutory regulation. 'Voluntary submission' might be considered a useful metaphor for the overall approach of regulators at this stage which is encouraging industry to adopt pharmacogenomics but not mandating it.

3 Pharmacogenomics in drug discovery and development

Whilst the voluntary data submissions process is a useful tool for the cutting edge of pharmacogenomics, there are aspects of the science which are well-established and as a result an increasing number of regulatory submissions include genomic data. This section reviews how pharmacogenomic data is dealt with in the setting of formal regulation. It reviews guidelines on requirements for data submissions, the impact on clinical trial design and the role of phase IV studies and enhanced pharmacovigilance.

Pharmaceutical companies are using genomic technologies at every stage of drug development:

- Phase one - Reducing risk by analysing inter-individual and population differences in drug metabolism
- Phase two - adjusting dose for metabolism and correlating efficacy with genotype
- Phase three - predicting efficacy and safety through the application of pharmacogenetic testing

This work may involve the use of well-established biomarkers such as the CYP450 genes or highly novel biomarkers identified by technology such as gene expression arrays.

Pharmacogenomic data submissions

Given the novel and complex nature of much pharmacogenomic data there is much concern in industry about how regulators will deal with it. Whilst pharmaceutical regulations require the submission of data on safety and effectiveness, the existing regulations predate pharmacogenomics and so do not contain explicit guidance on its use. What are the thresholds for inclusion of data in a regulatory submission? How should it be included and how much data will regulators require? What will be the status of data from highly novel biomarkers? These are the key questions which regulators and industry are beginning to address.

a) FDA

As stated earlier, the FDA's guidance on pharmacogenetic data submissions deals with their requirements for both voluntary submissions and regulatory decision-making. This guidance sets out:

- When sponsors should submit pharmacogenomic data
- Format and content of submissions
- How and when data will be used in regulatory decision-making

The FDA has not developed a new regulatory process for the use of genomic data in drug approvals, instead it has provided guidance on how genomic data can be used within the existing framework. The guidance seeks to allay industry fears about the FDA's approach to pharmacogenomic data by stressing that in general its applications will rarely be novel and the Agency's approach will build on existing practices. For instance, labeling requirements

concerning phenotypic indications for dosing and adverse effects are already common practice. Underpinning this approach is the Agency's recognition that most pharmacogenomic data is going to be probabilistic rather than highly predictive.

In most instances, a genotype or particular gene expression profile is likely to be one of a number of factors that affects the probability of an adverse event or a favorable response. For this reason, pharmacogenomic biomarkers can ordinarily be handled like other non-genomic predictive markers in the clinical arena.

FDA Pharmacogenomic Data Submissions Guidance

The need to submit data and the level of data required is dependent on two issues: how the data will be used and the status of the biomarker. Data that will be used to support the application - to guide dosing or which affects safety or effectiveness - must be reported in full regardless of the status of the biomarker. Data on biomarkers that are well-established should be reported even if the data is not being used in the application, albeit in this case it can be done in an abbreviated form. Data on more exploratory markers that are not used to support the application can be submitted via the VGDS process. The distinction between the two types of biomarker is made thus:

- Valid biomarker – robust analytical validity of test system and clear scientific consensus on the clinical validity of the biomarker
- Probable valid biomarker – robust analytical validity but with only apparent clinical validity, but data inconclusive and/or no consensus on, or independent verification of, its use

To supplement the VGDS process, the FDA has new systems for 'without prejudice' review of data within the formal regulatory system. The Agency has instituted what it terms exploratory INDs (sometimes called Phase 0 studies) using technology such as mass spectrometry to look at drug metabolism and pharmacokinetics at lower doses or in short duration exposures. There is also the new 'end of Phase IIA' meetings designed to help build better Phase III trials and avoid costly failures at the most expensive stage of development by giving the FDA far greater input into the design of the Phase III trial. In this process the FDA will look at the existing data and use mechanistic or empirical modelling techniques to simulate the Phase III trial. The results are shared with the sponsor on a non-binding basis.

This area is one in which there is a clear difference between the FDA and the EMEA. The recent IPTS report states that compulsory data submission has not been the subject of extensive discussion within the EMEA, in large part because of the nature of the 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 adverse events or lack of efficacy for a sub-population of patients.¹³

Biomarker validation

The FDA's guidance on data submissions makes the distinction between valid and probable biomarkers and highlights the fact that most pharmacogenomic biomarkers are insufficiently well-developed to be used in regulatory decision-making. As outlined earlier, the fundamental issue facing industry and regulators is that whilst it is hoped that the development of new biomarkers will assist in improving the drug development pipeline, the biomarker development pipeline is itself in trouble. The proportion of published candidate biomarkers which become qualified markers is very small. This is often attributed to problems around translational research, although recently Lee Hartwell has suggested that the problem is in the discovery phase.¹⁴ At a recent meeting Janet Woodcock of the FDA emphasised the following problems:

- Lack of understanding of scientific and regulatory pathway to qualification for use
- Lack of viable business model¹⁵

Whilst the drug development process is one in which biomarkers can become validated (discussed more fully in the section on drug/diagnostic co-development), there are significant economic costs attached to this work and in many instances there is little incentive for drug companies to carry out the work. There are a number of limitations to this model in terms of the scale of the research, i.e. pre-approval studies may be too small given: the commonly low frequency of critical variants; the often modest differences between groups and lack of prior knowledge of which are the significant variables; and the complex interaction affecting expression.¹⁶

In general, diagnostic companies also lack the financial incentive to carry out this work owing to problems around intellectual property (IP), reimbursement and the limited shelf-life of diagnostic products. Academic research is largely focused on the basic science level and there is inadequate funding, training or career opportunities for translational research in academia.

At a recent meeting one industry expert highlighted the following issues:

¹³ JRC-IPTS *Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU* (EC, 2006)

¹⁴ 'The biomarker bottleneck is in discovery, not validation, says Lee Hartwell' *GenomeWeb* 13/03/2006

¹⁵ Janet Woodcock, 'FDA Critical Path Initiative', presentation at National Cancer Policy Forum workshop on biomarker development, Washington DC, March 2006

¹⁶ Webster, C 'Regulatory pathways to qualify genomic biomarkers: what do we need?' Presentation at DIA Workshop on Genomic Biomarkers, 2005

- limited use of appropriate testing platforms in the market, which constrains uptake of new tests
- poor predictive value of heritable genetic markers, principally due to low penetrance
- biomarker development is an additional cost in drug development with no certainty of additional clinical benefit
- even where a biomarker may have clinical benefit it may have no economic value to the drug company.¹⁷

Faced with these problems, regulators are asking the question: if biomarkers can assist in the drug development process, what can be done to assist in their discovery and use, aside from issuing guidance on data submissions?

a) FDA

The possibility of acting as brokers to create public-private consortia is one option being developed by FDA. FDA co-sponsored a workshop on this subject with industry which was held in October 2005.

Because FDA lacks resources to fund research, the Agency sees collaborative work as central to the pursuit of its Critical Path agenda. This may involve joint projects with industry and academia, either individually or in groups, under Cooperative Research and Development Agreements (CRADAs).

The FDA has been one of the founding partners of the Critical Path Institute established by the University of Arizona and Stanford Research Institute International which will further translational research. Amongst its initial projects is a consortium for validation of toxicogenomic biomarkers and a prospective trial on Warfarin dosing (see section on Relabelling below).

Predictive Safety Testing Consortium

C-Path will act as a mediator between the eight pharma companies who are participating in the Predictive Safety Testing Public/Private Consortium. FDA were receiving toxicogenomic data from different companies, all using different markers and so they suggested the companies pool their data to identify the best methods. C-Path will act as a broker, companies will share their methods through C-Path and have them tested by other companies, C-Path will analyse the data and assess which methods they feel have been validated by replication and on that basis make recommendations to FDA.¹⁸

The industry body PhRMA has been heavily involved in establishing a public-private partnership for biomarker qualification – a tripartite consortium bringing together industry, the FDA and NIH. It has been established under the NIH foundation and can therefore receive Federal money and contributions from outside. Different syndicates will be formed under the umbrella of the consortium, each taking responsibility for a specific disease area –

¹⁷ Metcalfe, T Roche speaking at SACGHS, October 2005

¹⁸ 'The C-Path Institute's Ray Woosley on Critical Path Projects' in Pharmacogenomics Reporter 22/3/06

individual companies can participate alongside NIH academics. As with the VGDS process, the FDA will have an early view of pharmacogenomic data outside the formal regulatory process, and will be able to comment on the design of studies that will be acceptable for use in submissions.

Whilst the consortium will not be the only place where biomarkers are qualified, it will be able to aggregate data around a particular biomarker much faster than even a large company could on its own. Such a collaborative approach needs to deal with IP issues. Some proponents of collaboration from Pharma companies suggest that IP in biomarkers should be shared for the common good and that the more appropriate target for IP rights is not the biomarker but what you do with it – i.e. gaining faster approval for drugs – this will be discussed further in the section on industry. The FDA has proposed that data could be shared whilst companies could retain the IP rights to individual products, and academic bodies such as the C-Path Institute can provide a secure home for the sharing of proprietary information. The FDA/NCI/NIH consortium is also looking at other issues including the complex bureaucracy surrounding informed consent.¹⁹

b) EMEA

The EMEA has not gone as far as FDA in developing public-private consortia, but it explored role of biomarkers in drug development at a workshop in December 2005. This meeting brought together industry, academic researchers, clinicians and the regulators. It was an opportunity for the stakeholders to learn from each other on a range of scientific, technical and regulatory issues relating to biomarkers from discovery to clinical application. Approaches to biomarker validation were examined, as well as the influence of pharmacogenomics on new drug therapies. A follow-up meeting is now planned for some time in 2006 and the EMEA is now exploring the possibility of collaboration with FDA on genomic biomarkers, possibly in the field of toxicogenomics.

Clinical trial design

Pharmacogenomics is expected to have a major impact on the design of clinical trials. The premise behind pharmacogenetic research at the clinical stage of drug development is that a more discrete and suitable patient population can be selected. We have already outlined new mechanisms for influencing the design of clinical trials, such as the exploratory INDs and ‘end of Phase IIA’ meetings introduced by the FDA. There is, furthermore, a great deal of work on new statistical approaches, such as the use of Bayesian statistical models to improve prediction of clinical trials outcome. Both the FDA and the EMEA have recruited new staff to address statistical challenges arising. However, whilst there is a great deal of discussion around the issues of clinical trial design (the issue has come up at every single VGDS meeting held by FDA), particularly the concept of adaptive trial design, nevertheless there has not been any major change in policy. No significant changes have been proposed in the guidance documents issued thus far, either by FDA or other agencies. Review of trial design is currently taking place on a case-by-case basis. Some commentators suggest that there is thus far a certain caution in the FDA’s approach to this issue .

¹⁹ Janet Woodcock, Deputy Commissioner, FDA at National Cancer Policy Forum workshop on biomarker development, Washington DC, March 2006

“What is lacking today is leadership in establishing specific guidelines for the design and analysis of adequate clinical trials that test new treatments in patient populations pre-defined based on completely specified diagnostic classifiers.”²⁰

Richard Simon, National Cancer Institute

Phase IV studies and post-marketing surveillance

One of the main benefits that it is hoped that pharmacogenomics can bring is a greater understanding of adverse events. The number of people exposed to a drug during clinical trials is a tiny proportion of those who will eventually receive the treatment once it has been approved. Yet the regulatory system is largely geared to assessing this limited data which is inadequate for understanding adverse events (AEs), especially the rarer idiosyncratic AEs.

There is considerable scope for enhanced post marketing surveillance to understand the genomic basis of adverse events (and indeed other aspects of drug response). Yet once a drug has been approved, manufacturers have little incentive to carry out further research.

Since 1993 the FDA has had the authority to grant accelerated approval for drugs targeting life-threatening conditions, usually on the basis of surrogate endpoint data. In return for fast-track approval companies must carry out post-marketing studies (but the focus here is on effectiveness rather than safety). There has also been a steady increase in the use of Phase IV studies more generally, a development which has made industry unhappy. However, some companies are now suggesting that a greater emphasis on Phase IV would be acceptable, if it were on the basis of accelerated conditional approval at Phase III. Some believe that companies will only conduct population stratification studies for differential activity in subpopulation studies if they have the kind of powerful incentive that this model would provide.

Whether regulators will develop a model like this when there is public and political concern about drug safety is questionable. Furthermore, such a move would have to address some long-standing problems with post-marketing surveillance. Post-marketing surveillance has been focused on passive reception of adverse event reports. There are a number of structural issues (such as fear of liability suits) which meant that the US generally has a poor record in adverse event reporting. Even the mandated reporting of vaccine safety events has been poor. Furthermore, formal Phase IV studies, mandated as part of the approval, are often not carried out – a 2003 study revealed that only 20% of the Phase IV studies agreed to since 1991 had been completed and 45% had not yet begun.²¹ Practical considerations relating to access to data must be addressed, as well as questions of cost and informed consent.

²⁰ Simon, R ‘Clinical trial design and biomarker-based tumour classification systems’ presented at National Cancer Policy Forum workshop on biomarker development, Washington DC, March 2006

²¹ Industry reneges on postmarketing trial commitments *Nature Biotechnology* July 2003

There is currently considerable concern about drug safety and a variety of proposals for enhanced regulation of marketed drugs, including enhanced postmarketing surveillance and an independent Drug Safety Oversight Board within FDA. FDA are exploring some of these issues through the Critical Path, the C-Path Institute has partnered with an Arizona pharmacy chain to create a public network for reporting adverse events, which aims to help FDA improve its drug safety monitoring system.

A forthcoming paper by Barbara Evans and David Flockhart argues that FDA postmarketing surveillance has been limited in its scope.

FDA's post-market monitoring and reporting emphasize collection of data that would have been relevant during pre-market approval (e.g., adverse events related to drug use), rather than creation of new information specifically relevant to safe clinical use (e.g., data explaining why some people react badly, data identifying ways to spot those people before drugs are administered, and data identifying the best procedures to detect and mitigate the harms that do occur.)²²

They suggest that fundamental reform will be required to create an infrastructure which will capture the full range of data necessary to ensure the safe use of drugs and promote clinical compliance with the growing body of drug safety data. They believe that this work will require concerted action by health insurers, healthcare providers and physicians, as responsibility for this extends beyond FDA and drug manufacturers. This argument highlights the role of a variety of gatekeepers and is one we will return to again, particularly in our discussion of in-house tests.

International harmonisation

As noted above the FDA and EMEA have held joint VGDS/pharmacogenomic briefing meetings and further joint meetings are planned. The two agencies are now working with their Japanese colleagues in PMDA on a broader harmonisation process through the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). The ICH was established in 1990 with the aim of rationalizing aspects of the highly divergent regulatory frameworks of the countries involved. It began its work with an initial focus on technical guidelines, but more recently work has been undertaken on the format and content of regulatory submissions. Its work is conducted through major international conferences held every few years, and between conferences progress is facilitated through smaller international meetings, usually held twice a year.

Pharmacogenomics is on the agenda of the next ICH conference (to be held in Vienna in 2007) as part of a broader discussion of new technologies such as gene therapy. The ICH process on pharmacogenomics began with an informal session in May 2005 and then a further informal meeting in November. Formal work will begin at the next session in June 2006 in Japan, around the initial topic of terminology, a logical starting point. Future work might

²² Evans, B and Flockhart, D 'The unfinished business of US drug regulation' forthcoming paper

include areas such as the format and content of pharmacogenomic submissions and the design of pharmacogenomic clinical trials.

Analysis

It is possible to envisage that in the future, particularly in the context of a greater emphasis on safety data, all new drugs will require a pharmacogenomic section included in their approval submissions but for now such data is likely to be mandatory only in certain circumstances. The shift from 'voluntary submission' to mandatory data requirements is one of the most difficult policy issue for regulators. Would such a move be the most effective way to promote pharmacogenomics? Does the science justify such a shift, and would it have a positive impact or would the additional costs simply lead to a further decline in the productivity of the pharma pipeline? Should pharma be required to give up the blockbuster model, for instance, if a clinical trial where the drug shows an 'acceptable' response rate, should there nevertheless be pharmacogenomic investigation of whether the response is largely in a sub-population?

An alternative policy is to focus on the science by facilitating research on pharmacogenomic biomarkers, thus allowing more time for industry to become familiar with the new paradigm and for the science itself to mature.

Similarly, a greater role for post-marketing surveillance would be a major shift in policy but this time one which would require concerted action by a range of players.

4 Pharmacogenomics in clinical practice

We are still in a situation where the bulk of genomic data amassed during drug development is not shared with regulators, clinicians or the public, and does not affect the approval or clinical use of new drugs. However, this is changing – a growing proportion of submissions contain genomic data and there is a related increase in the number of new approvals where the drug label contains genomic data (furthermore, the transparency of pharmacogenomic data may be affected by the establishment of public registries for clinical trials). On the diagnostics side the last 18 months has seen major developments with the first approval of a pharmacogenetic microarray (the Roche Amplichip) and a growing number of CYP450 competitor products expected to file for approval in 2006. There is also considerable innovation in the in-house testing sector with companies such as Genomic Health and Agendia launching new gene expression tests in the cancer field.

The scientific challenges in clinical application of pharmacogenomic data remain the same – the complexity of the underlying molecular biology of drug response; the robustness of the testing platforms, and the statistical challenges; in essence the quality of testing (both the robustness of the technology and the quality of the clinical data). But the regulatory focus is different. As pharmacogenomics enters clinical practice, the fundamental regulatory challenge is ensuring that clinicians and patients understand enough about the utility and predictive value of testing to make informed decisions about its use in treatment.

For those charged with the regulation of diagnostics, many of the issues raised are not new – the quality of information on drug and device labels, the role of clinical evaluation in device approval; and the lack of a level regulatory playing field between test kits and in-house tests – but pharmacogenomics, by linking diagnosis/prognosis more closely to treatment, raises the stakes.

Pharmacogenomic testing is part of the broader field of molecular diagnostics market, the fastest growing sector of the IVD industry. The level of innovation in molecular diagnostics far outstrips any other sector of IVD, particularly in the area of identifying new biomarkers. There is also a growing view amongst many stakeholders that for a variety of reasons - economic pressures on the healthcare system, the rise of evidence-based medicine, and the lessons of past failures – there is a need to improve the processes used to evaluate new diagnostic tests. The controversy surrounding the utility of PSA testing, and the harms that may have arisen from its inappropriate use, is an example which stakeholders have referred to on several occasions.

Labelling and relabelling

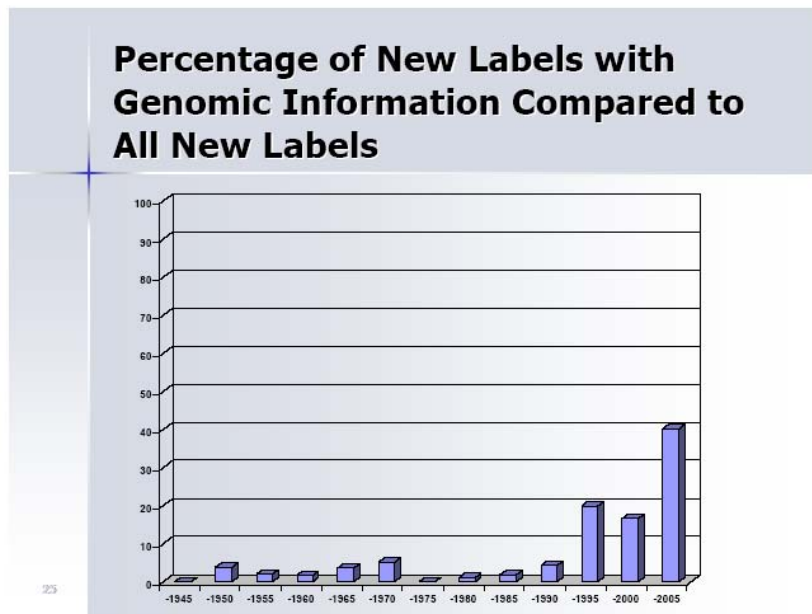
a) Labelling

The adoption of pharmacogenomic testing in clinical practice has been slow and patchy at best. Some have suggested that one factor may be the lack of clear direction from

regulators.²³ Regulators who wish to encourage its adoption need to consider the quality of advice offered to doctors and laboratory professionals in the drug labels.

The regulatory question here is about the quality of evidence and about the quality of information provided to doctors and patients via the drug label.

Both the FDA and EMEA report that an increasing number of new approvals contain pharmacogenomic information in the drug label. For instance, the EMEA reports that 20% of new products contain genomic data in their labels and labels with recommendations for genetic profiling will likely be seen from EMEA by the end of the year.



Figures from FDA²⁴

In the US there is already genomic guidance on about 60 different drug labels. Most of it relates to the role of the CYP450 genes. Its helpfulness and clarity for physician varies; in general, the more recent the label, the more informative the guidance. But many of the older labels do not provide clear guidance to physicians, giving some genomic information but no guidance on how and whether a test may be helpful. Allan Rudman, Associate Director at OCPB at FDA is leading a review of this group of labels to see if they can be improved. EMEA are undertaking a review of all cancer therapeutics approved since 2000, looking at the genomic information in the evaluative data and on the label with a view to standardising descriptions of predictive value and the criteria for clinical recommendations.

²³ JRC-IPTS *Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU* (EC, 2006)

²⁴ Felix Frueh, FDA presentation at DIA Europe, Paris 2006

b) Relabelling

Enhancing the use of pharmacogenomic data in the labels of approved drugs is a central part of the FDA's strategic plan.²⁵ Recent relabelling decisions and recommendations include:

- 2003 - Straterra - relabelled to include data on CYP2D6
- 2003 - Thiopurines - relabelled to include data on TPMT
- 2004 - Irinotecan - relabelled to include data on UGT1A1
- 2005 - Warfarin - recommendation for inclusion of data on CYP2C9 and VKORC1

Thus far, labelling updates have been advisory/cautionary rather than mandatory. This approach probably reflects both the limitations of the clinical data available to support the use of a test and the adoption of a cautious incremental approach in a new regulatory area.

Irinotecan

The colorectal cancer drug irinotecan (Campostar, Pfizer) was relabelled after growing evidence that severe adverse events in some patients were associated with a specific allele of the UGT1A1 gene. Whilst there is insufficient data to make precise dosing recommendations, it was felt that the data on a heightened risk of neutropenia was sufficiently strong to justify relabelling.

However, the prospect of stronger relabelling guidance has been raised by the FDA's Clinical Pharmacology Subcommittee, which in November 2005 voted to recommend that Warfarin be relabelled to reflect the ability of genetic tests to guide dosing. There was unanimous agreement that there was sufficient evidence to recommend that lower doses of Warfarin be given to patients with genetic variations in CYP2C9 [and in the VKORC1 gene] that lead to reduced activities and that genotyping patients in the induction phase of Warfarin therapy would reduce adverse events and improve achievement of stable INR in patients with genetic variations in CYP2C9 [and in the VKORC1 gene]. There was an 8 to 2 majority in favour of relabelling to include genomic and testing information. It is expected that FDA will follow this advice but it remains to be seen how strong the labelling recommendation will be.

One of the issues besetting the relabelling process is that the data on which to base decisions is derived from retrospective studies. Whilst it is possible to improve the value of such studies by the use of meta-analyses, the Warfarin recommendation has highlighted the potential value of prospective studies to give clearer data on which to base dosage recommendations.

The C-Path Institute are undertaking a prospective trial with the University of Utah. The trial has already begun, funded by C-Path and Utah but with the expectation of Federal funding in the next few months under the Collaborative Cardiovascular Drug Safety and Biomarker Research Program.²⁶

²⁵ Lesko, L 'Managing regulatory uncertainty: USA-FDA perspectives and strategies', presentation at OECD workshop on pharmacogenomics, Rome, October 2005, accessed at: <http://www.oecd.org/dataoecd/34/60/35641440.pdf>

²⁶ 'The C-Path Institute's Ray Woosley on Critical Path Projects' in Pharmacogenomics Reporter 22/3/06

Europe

European regulators have been far more reluctant to relabel than the FDA. EMEA's authority in this area is perhaps limited as it would appear that where approval was given on a state-by-state basis then updating of the drug label is the responsibility of individual member states, but relabelling to include pharmacogenomic data does not seem to be a priority issue for their regulatory agencies.

Drug/Test co-development

Administrative frameworks already exist for approval of drug-test combinations and have been used successfully by FDA and EMEA in the case of Herceptin. The example of Herceptin raises an important regulatory issue which is the degree to which the drug approval process will drive device approval. In the case of Herceptin there was some concern about the performance of the first generation of the test which missed around 20% of patients, in large part due to ambiguities about the cut-off, but the view was that the overall benefit to patients was sufficient to accept this problem and have it dealt with post-market.

a) FDA

The FDA initiated its policy work in this area with a co-sponsored workshop aimed at developing draft guidance that would address the approval pathway for a drug combined with a pharmacogenomic test. An initial concept paper was issued in April 2005 for public consultation and now a draft guidance paper is being prepared which should be issued some time in 2006.

The co-development concept paper sets out what might be considered the optimum process for developing a drug and test together. In this ideal model the biomarker is part of drug development from inception and the clinical phase of drug development will demonstrate the clinical value of the diagnostic test allowing the drug to be cross-labeled for use with the diagnostic. Ideally, by end of Phase II the utility of the biomarker should be well established and Phase III will allow the development of a diagnostic test kit that will be ready for approval at the same time as the drug.

This guidance outlines the scientific issues relating to analytical and clinical validation of a pharmacogenomic test and the evaluation of clinical utility. It makes the important point that when a drug is linked to a test then their performance is interdependent. Whilst it is of course central to pharmacogenomics that a test may improve the safety and efficacy of a drug through more accurate targeting to a specific population, it is less often discussed that the performance of the drug will also affect the validity and utility of the test; that is to say that drug response is equivalent to prevalence for a diagnostic, so variations in drug response, like variations in prevalence, will affect the predictive value of a positive and negative result.

A draft guidance paper which builds on the feedback received from the concept paper is now being prepared and should be available later in 2006. It is expected that the draft will focus more on clinical aspects and address more fully the question of how to integrate diagnostic development with the drug development process.

Europe

Like the FDA, the EMEA has approved drugs co-developed with tests (Herceptin), but unlike the FDA, the EMEA does not have a diagnostics division and has no legal authority over the regulation of diagnostic tests. Authority for the regulation of medical devices under the European IVD Directive, resides at the member state level. Therefore whilst the EMEA can evaluate the performance of a test co-developed with a drug, and can include strong recommendations for the use of testing as part of the drug label, they cannot mandate the use of a particular test kit. Furthermore, this regulatory gap means that the EMEA do not feel empowered to issue guidance on co-development.

No action has been taken at the European level by the expert groups which guide device regulation and whilst the IVD Directive permits individual member states to take action where they deem it necessary, none have done so in relation to pharmacogenomics. EMEA officials, committed to the ideal of harmonisation through the ICH process, would prefer to avoid a situation where individual member states take action

Device approvals and guidance

Not all pharmacogenomic tests will come to market as co-diagnostics for new drug approvals. Many may have a more general application to a range of drugs like the Roche CYP450 Amplichip; be linked to an established therapeutic, like the UGT1A1 test developed by Third Wave for use with Irinotecan; or have a more general prognostic utility, such as Genomic Health's Oncotype DX.

The first pharmacogenetic devices were approved in the US last 18 months: the Roche CYP450 Amplichip, a microarray device for CYP450 testing and more recently a test device for UGT1A1 (following the Irinotecan relabelling) produced by Third Wave. The Roche Amplichip has also been CE-marked for use in Europe.

To understand the differences between the European and American approaches it is perhaps useful to describe how pharmacogenomic tests fit into the broader system of IVD regulation. We shall look at three issues: the kind of evaluation which regulators undertake for new tests; the way in which risk classification affects the level of scrutiny for pharmacogenetic tests; and the relationship between device regulation and the regulation of in-house tests.

Risk classification of pharmacogenetic tests

The regulatory systems for IVD tests are predicated on the principle of risk management and a fundamental aspect of this is risk classification. The level of oversight required for a given diagnostic device is determined by its risk classification; the greater the risks posed by the test, then the higher the level of scrutiny. For instance, in the US system a low-risk (Class I) device is exempt from pre-market review, but a high-risk (Class III) device is subject to detailed scrutiny of both its analytic performance and clinical validity.

To understand risk classification one must understand the criteria used to assign risk. These include

- the role of the test in clinical decision-making i.e. the impact of an incorrect result on the individual patient, or, in the case of infectious disease, on public health. In Australia and Canada this is largely based on the severity of the disease, but the degree of reliance on the result (is it a 'stand-alone' test or are there other tests to confirm the result) is also an issue (highlighted in the European system);
- novelty - the US system places considerable emphasis on novelty (defined by the device's intended use), so all devices with new intended uses are high-risk by default. However, since the passage of the FDA Modernization Act in 1997 these can then be reclassified as moderate risk on appeal (usually decided on the basis of impact on clinical management, see above);
- user competence – point-of-care devices for doctors and nurses and over-the-counter self-testing kits for the general public are often treated differently to devices for use by skilled lab professionals, on the basis that the former need greater direction to ensure the safe and effective use of the device (including interpretation of the results).

Risk classification is generally done on a case-by-case basis but with reference to classification schema or guidance and the logic of previous classification decisions which set out the likely classification for a new test. However, although risk classification is universal there is some variation in the systems used and their application to pharmacogenomic tests.

a) USA

In the US system tests which have “substantial importance for prevention of impairment of health, or that have a potential unreasonable risk of illness or injury” are Class III.²⁷ Also, all novel devices (those without a predicate device on the market) are deemed to be Class III, but manufacturers can appeal for downgrading to Class II. This is a common and generally successful process. Industry suggest that at one point it seemed that the most likely approval route for pharmacogenomic tests would be Pre-Market Approval as Class III devices. However, the Roche CYP450 Amplichip (approved December 2004) and the UGT1A1 device (approved Summer 2005) were both Class II 510(k) approvals, a quicker, cheaper and more flexible form of approval and FDA's most recent guidance states that they expect this to be the route for most pharmacogenetic and genetic tests.²⁸ This guidance has been welcomed by many in industry both for its clarity and simplicity. Since a 510(k) review is generally far less costly and time-consuming than Class III PMA approval route (however, it should be noted that FDA has considerable latitude in the degree of scrutiny required for 510(K) approval).

510(K) approvals are based on the idea that novel devices can be approved as Class II if they are low/moderate risk, or if their risk can be mitigated by special controls – including performance standards, postmarket surveillance and guidance standards - to ensure their safety and effectiveness. The Roche CYP450 Amplichip was approved with two such 'special controls' guidances and these now provide general guidelines for the submission of similar devices (thus the UGT1A1 test cited the Amplichip as its predicate device).

²⁷ Mansfield, E et al 'Food and Drug Administration Regulation of *in Vitro* Diagnostic Devices' in Journal of Molecular Diagnostics, Vol. 7, No. 1, 2005

²⁸ FDA, CDRH February, 2006 Pharmacogenetic tests and genetic tests for heritable markers. Draft guidance for industry and FDA staff p.2

b) Europe

Classification in the IVD Directive resembles the US system in that there are high-risk tests which require greater scrutiny and low-risk tests which are exempt from pre-market review (in the European system the manufacturers *self-certify* for low risk tests, that is they attach the CE mark which declares conformity with the essential requirements of the Directive). High risk tests are in Annex II of the Directive and there are two categories – List A which are largely tests used in blood screening including HIV and hepatitis and List B which is a more heterogeneous group and includes tests for toxoplasmosis. Annex II tests are evaluated by an independent third party (termed Notified Body) rather than the regulatory agency of a member state, prior to being CE marked.

Amongst those tests in Annex II List B is HLA, which is used to screen for patients at greatly increased risk of adverse reactions to the HIV drug Abacavir and a test for PKU, a heritable disorder. However, so far new pharmacogenomic tests that have come onto the market, such as the Roche CYP450 Amplichip and the Nanogen/Jurilab DrugMet test (also for CYP450 genes) have all been self-certified. Whereas in the US system classification is on a case-by-case basis and with an assumption that novel tests require greater scrutiny and are therefore high-risk, in the European system, the assumption is that a new test is low risk.

Indeed, the mechanism for adding a test to Annex II List B is extremely cumbersome and has never been used. In deciding whether new tests might be added to List B, due consideration must be given to three criteria: the degree of reliance on the test result; the likely impact of incorrect results and the potential role for the notified body in evaluating the devices performance. Member states make a proposal to the European Commission and this is then submitted by the Commission to the Committee on Medical Devices. As regards the likelihood of agreement to such a proposal amongst the Committee, this may not be straightforward – there was a great deal of disagreement on what should be included in this list initially, so it is perhaps not surprising that there have been no proposals so far for additions to Annex II List B.

Risk classification in the US system uses two forms of criteria – the impact on the patient and the novelty of the device. In the European system the novelty of the device is not used as a criterion for risk classification, however, there is another risk management tool for novel devices. Articles 10 and 11 of the Directive place a special obligation on manufacturers to inform competent authorities when they are introducing “new products” i.e. products which are new with regard to “the technology used and the substances to be analysed or other parameters ... this is true in particular of high-density DNA probe devices (known as micro-chips) used in genetic screening”. Such new products are subject to special vigilance procedure whereby the regulator can request data on the device’s performance in the field any time in the first two years after it is placed on the market. It is not known if these powers have been used by the regulatory authorities of member states.

c) Canada

Canada has a four-class system and all genetic tests are Class III including all devices intended to be used for pharmacogenomic testing. These require a pre-market scientific assessment of the safety and effectiveness by the Medical Devices Bureau. The risk classification is based on

the fact that pharmacogenetic tests need greater pre-market scrutiny because they “may have profound impact on the safety and effectiveness of the drug for which the assay/test is performed.”

d) Australia

Australia has taken on Canada’s model of a four-class system but it divides genetic tests between Class II (relatively low risk tests such as for Factor V Leiden) and Class III (tests such as for Huntington’s Disease where the impact of the test result is deemed to be greater). The Her2/neu test for Herceptin is Class III and classification of any similar new pharmacogenomic tests would likely be in this category, although classification will be done on a case-by-case basis and will depend on the impact of the specific test on public health and risk to the individual.

Clinical evaluation of new tests

The safety and effectiveness of diagnostic tests is dependent on their sensitivity, specificity and predictive value. Harms can arise as a result of false positive and false negative results. For instance, pharmacogenomic tests may have a direct impact on decisions to treat and dosing levels and their accuracy is therefore of great importance. False results may arise as a result of poor analytic validity (the accuracy of the test in identifying the gene when it is present and in giving a negative result when it is absent) or from poor clinical validity (the strength of the relationship between the genotype and the phenotype).

Clinical validation of pharmacogenomic tests can be difficult because the genotype/phenotype relationship is often complex. Drug response will often be determined by more than one gene leading to significant phenotypic variability in response, depending on which combination of the particular genes carry functional polymorphisms. As well as the polygenic nature of drug responses, there is the complicating factor of non-genetic sources of inter-individual variation, including liver and kidney function, ageing, and whether the patient is on other medication. There is also the issue of ethnic variation to take into account, for instance, the distribution of the variant alleles for P450s differs markedly between ethnic groups, a fact which helps to explain global variations in treatment responses to many drugs.

All these factors make the clinical evaluation of pharmacogenetic tests a complex challenge. The safe and effective use of pharmacogenomic tests will depend on the thorough evaluation of new tests. As noted in the introduction, evaluation can take place at the three levels of oversight identified – licensing, health technology assessment and clinical governance. However, the focus of this report is licensing, and here there are significant differences in how regulatory systems deal with the issue of clinical evaluation, in particular the question of whether it is obligatory to submit data on the clinical validity of a test.

a) USA

Tests which are Class I are exempt from pre-market review. All other tests go through a pre-market review process which encompasses both analytic validation and clinical validation. The scope is made clear in the recent FDA guidance on pharmacogenetic tests:

“The intended use of the device for which approval or clearance is sought should specify the marker the device is intended to measure, the clinical purpose of measuring the marker, and the populations to which the device is targeted, where appropriate.”²⁹”

For a Class II device which goes through the de novo 510(K) approval process, clinical validation may be done through citation of literature or a professional practice standard, the clinical validity of the device may be compared to a reference method or to clinical diagnosis. Where the test uses a novel marker then the comparator will be clinical diagnosis and the manufacturer will be required to undertake clinical trials. For both processes the standard is the same – the device should be ‘safe and effective’. For the FDA the risk/benefit analysis of IVDs is fundamentally different to that for drugs, because with diagnostics safety and effectiveness are completely interlinked. A drug may be highly effective because it treats the disease it targets yet be unsafe because of toxicity. Ineffective devices, those with low predictive value, are thus also unsafe because their ineffectiveness leads to the harms arising from false positive and negative results.

However, the issue of clinical evaluation is complex because clinical validity will vary according to the intended use.

“Some devices may have multiple intended uses. We encourage separate applications for each intended use, if each has unique and separate supporting studies; however, in certain cases of pharmacogenetic tests, we would consider application of test results in multiple therapeutic settings as a single intended use. For example, determination of CYP2D6 alleles for the purpose of providing information to aid in drug selection, without reference to a particular drug, would be an appropriate single intended use, given that it is well known that CYP2D6 affects the metabolism of many drugs.”³⁰

In some cases manufacturers can deal with the complexities of multiple use by seeking approval for the least high-risk use and then allowing laboratories to practise their clinical freedom to use the test in other contexts, without them having to actively promote such use. However, with pharmacogenomic testing this may be more difficult. Clinical uptake has been slow and so test manufacturers who wish to make a market for CYP450 testing will have to make the clinical case for the testing, as such it is likely that their range of drug-specific claims will widen as an increasing number of tests are relabeled. Will they be expected to make new submissions for each new claim? The FDA’s draft guidance also states that:

²⁹ FDA - Pharmacogenetic Tests and Genetic Tests for Heritable Markers – Draft guidance for industry and FDA staff (2006)

³⁰ FDA - Pharmacogenetic Tests and Genetic Tests for Heritable Markers – Draft guidance for industry and FDA staff (2006)

“different uses might have different risk profiles, and therefore might have separate intended use claims and submissions. In these cases, you should provide appropriate data to support each claimed intended use.”³¹

Steve Gutman, Director of OIVD has outlined that this may be an issue with the Roche CYP450 Amplichip:

“Certainly if there were specific claims and specific performance parameters that were to be generated on top of either of these assays, we would probably like to be revisited with more submissions. That would probably be okay for UGT IAI since it doesn't seem to be an infinite spectrum of possibilities. That might be more problematic for the Roche Amplichip since about 20 percent of medications in the country theoretically could be impacted.”³²

The situation is further complicated by the possibility of polygenic relabelling decisions, as in the case of Warfarin where CYP450 genes and another genes VKORC1 are both involved. FDA have not decided how to deal with this problem but one option would be some arrangement where the Office of Combination Products could ensure that relabelling of drugs could be tied to relabelling of affected test kits, where the test manufacturers wished this to be done.

Industry has tried to move FDA to a new system in which analytic validity is sufficient to allow a device on to the market. Proposed formally as the IVAT model, the idea has been resisted by FDA. OIVD Director Steve Gutman outlined three major problems with the idea at a presentation in 2003:

- How to delineate between investigational and clinical phase of use?
- How to classify without specific indications for use?
- How to address clinical validation?³³

However, in practice it is possible for device manufacturers to sell some elements of a pharmacogenomic test without having to undergo clinical evaluation by FDA. Under the Analyte Specific Reagent rule, manufacturers can sell the reagents for detecting particular genes as Class I devices. This rule was introduced to bring some measure of control to the proliferation of reagents being sold to laboratories to make their own in-house tests. Manufacturers must now register with FDA and follow GMP guidelines but there is no evaluation of their ASRs and because of this they are not permitted to make performance claims for either the analytic or clinical validity of their devices. In effect, the management of

³¹ FDA - Pharmacogenetic Tests and Genetic Tests for Heritable Markers – Draft guidance for industry and FDA staff (2006)

³² Gutman, S at SACGHS October 2005

³³ Steve Gutman, OIVD October 2003 presentation at FDA/Industry roundtable meeting

risk is pushed downstream to laboratories who use the ASRs to make their own in-house tests (only laboratories which are authorised to conduct ‘high-complexity’ tests are permitted to use ASRs. This issue will be explored further in the section on in-house tests below.

b) Canada

As Class III devices, pharmacogenomic tests will be subject to full pre-market review. The requirement for data on clinical validity in Health Canada’s recent draft guidance on pharmacogenomic data submissions, which states that “Once a sponsor has established the analytical validity of a test, its clinical validity and utility can be established only by testing in human populations. Every study based on pharmacogenomic data should provide evidence that the performance characteristics of the test used were satisfactorily validated.”³⁴

However, where a manufacturer makes no clinical claims for their device, then it may be possible for them to provide only data on analytic validity. Like FDA’s ASRs, such a device would be considered Class I and thus subject to far less scrutiny. How this might work in practice may need to be tested by actual submission for approval, since the Canadian Medical devices Bureau (MDB) seem to be placing greater emphasis on clinical validity data than European regulators enforcing the IVD Directive.

c) Europe

There would seem to be considerable ambiguity regarding the degree to which there is an obligation on manufacturers to provide data on clinical validity under the IVD Directive. The general consensus is that there is no such obligation; manufacturers are *obliged* to provide data only on analytic validity, but when a manufacturer makes clinical claims for a device, then they must provide data to support those claims.

The view that the Directive’s obligations are limited to analytic validity has been challenged by some who suggest that, if faithfully interpreted, it may place greater emphasis on clinical effectiveness and may, in practice, require performance data on each test apparatus ‘in its intended use in patients’ in order to demonstrate compliance with many of the Directive’s requirements for safety and performance evaluation.³⁵

The IVD Directive sets out a series of six essential requirements concerning safety, quality and performance which all IVDs must comply with before being CE marked and placed on the market. Requirement Three states that devices must meet the manufacturer’s specifications, taking into account “the generally acknowledged state of the art”. Performance criteria that may be appropriate include “**analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity**”. Common usage of these terms would suggest that analytical sensitivity and specificity refer to analytic validity and diagnostic sensitivity and diagnostic specificity refer to clinical validity. It is presumably the fact that the manufacturer may determine which criteria are appropriate which has led to the common view held by both industry and regulators, that the Directive only requires data on analytical validity.

³⁴ Health Canada Draft Guidance Document: Submission of Pharmacogenomic Information (March 2006) http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demande/guides/pharmaco/draft_pharmaco_ebauche_e.html

³⁵ Higson, G *Medical device safety – the regulation of medical devices for public health and safety* (Bristol, Institute of Physics, 2002) p49

d) Australia

Australia's new regulatory framework draws heavily on the European model in its requirements for performance evaluation, and shares the same focus on data on analytic validity, but again claims regarding clinical validity must be supported with data.

There is a tension inherent in this – the Australian's more sophisticated risk classification system is based on intended clinical use so manufacturers who wish to evade the more stringent scrutiny attached to a higher risk device could presumably do so by not making any clinical claims for the device, leaving these to be inferred by users.

Regulation of in-house tests

Genetic testing is characterised by a high degree of dependence on tests developed in-house by laboratories. In general the regulation of laboratory tests is focused on quality assurance of laboratory procedures and the analytical accuracy of laboratory testing; clinical validation of in-house tests is rarely mandatory.

The regulatory status of such tests is ambiguous and has been the focus of much debate, particularly in the USA, where it is widely acknowledged that companies sometimes choose to circumvent FDA regulation by building a clinical laboratory to offer their test rather than selling diagnostic kits.³⁶

The FDA's ambivalence about this state of affairs is expressed in a recent paper by the Director of OIVD and one of his senior colleagues, in which they acknowledged both the role in-house tests have played in diagnostic innovation, and the importance of CLIA regulation in ensuring the analytical accuracy of tests, but nevertheless highlighted a number of serious concerns:

- The transition from research to clinical use phase of test use is not well defined under CLIA
- Device specific premarket evaluation is not performed under CLIA
- CLIA is focused at analytical but not clinical test validation.³⁷

Broadly speaking there are two possible solutions to the lack of a level regulatory playing field at the level of statutory control. One is to extend the activities of device regulators to encompass the in-house testing sector; the second is for the regulation of laboratories to be broadened to encompass many of the aspects of device regulation which are currently absent. Both these solutions have been either proposed or adopted in a number of countries. A further solution is to use non-statutory mechanisms to oversee in-house tests.

³⁶ Borchardt, P and Fernandez, D 'Pharmacogenomics: an in-house advantage?' in *Pharmalicensing.com* 29 November 2005 Accessed at: http://pharmalicensing.com/articles/disp/1133196003_438b32e3548ea

³⁷ Hackett, J and Gutman, S 'Introduction to the Food and Drug Administration (FDA) regulatory process' in *Journal of Proteome Research* 2005, 4, 1110-1113

The use of in-house developed tests is an established part of pathology. It is useful to draw a distinction between the very common use of in-house tests for research and development - where a novel biomarker or a novel application for an existing biomarker is first developed in-house before eventually being developed into a diagnostic kit - and those areas of clinical pathology where, for a variety of reasons, testing remains based on in-house developed tests more or less permanently. This may be because the complexity of the testing process requires skill which cannot be standardised in a kit, or the niche nature of the test means that there is no commercial market to sustain kit development. Both factors have meant that genetic testing for heritable markers is almost entirely based on in-house testing, the issues this raises are not confined to genetic tests, although the debate has focused on genetic tests (mainly because of the wider ELSI concerns around these tests), in-house developed tests are also common in other areas, for instance immuno-histochemical staining.

It is also important to distinguish between the three types of in-house (sometimes referred to as 'homebrew') tests:

- a test created from scratch in the laboratory;
- a test where the components are bought in and then assembled by the laboratory;
- a test kit which is modified by the laboratory.

Given the relative ease and speed with which an in-house test can be developed, it is not surprising that it is generally considered the major source of innovation in clinical testing, including pharmacogenomic tests. This question of speed of innovation is highly relevant in the case of drug-device co-development. It will often be unrealistic to expect that a robust test kit will be ready for approval at the same time as the drug. Thus regulators may have to approve the drug in combination with an in-house test. A precedent for this has already been set in the US by the FDA.

Where in-house testing is a mainstay of testing provision, and the bulk of tests carried out are well-established ones, for which there is professional consensus on the appropriate use of the test, then the major regulatory concern is around the effectiveness of quality assurance procedures. Concerns around the quality of in-house testing for Her2 exemplify this issue.³⁸ However, pharmacogenomic testing is may be an area where in-house tests are used at the innovation stage, but where there will be sufficient demand that in-house tests are then developed into kits by test manufacturers. Certainly the number of companies preparing to bring CYP450 test kits to market to compete with the Amplichip suggests widespread industry optimism that there may be a large enough market for test manufacturers.

The regulatory approach which is adopted must therefore take into account the possible impact of greater regulation on the level of innovation. Although the broad debate about the regulation of molecular genetic testing labs is more focused on general quality assurance procedures, the discussion below will focus on the issue of the pre-market evaluation of new tests, an issue of at least equal concern to QA, where the use of in-house tests is highly innovative.

³⁸ For further discussion of this important area see JRC-IPTS *Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU* (EC, 2006)

a) USA

At present the regulation of in-house tests is governed by the CLIA regulations and administered by Centers for Medicare and Medicaid Services (CMS). The Secretary's Advisory Committee on Genetic Testing (SACGT) recommended that the regulation of laboratory testing should be enhanced to ensure that labs provide data on the clinical validity of their tests. In recent years CLIA, the advisory committee which has oversight of the CLIA regulations which govern laboratories, has been working to introduce a genetic testing specialty under CLIA to develop new standards for genetic testing. It issued a Notice of Intent as a consultation document in 2000, which included proposals to extend test assessment to clinical validity, and oversight to areas such as informed consent. Both these proposals have been controversial attracting both considerable support and much opposition. CLIA is now close to publishing a proposed rulemaking for consultation. However, the clinical validation aspect of this rule will not be for pre-market evaluation, instead data on clinical validity will be examined at the time of the laboratory inspection. Such a system has already been put in place by the College of American Pathologists (CAP), one of the third-party bodies whose inspections are recognised by CMS as equivalent to CLIA. Given that inspections only take place every two years, then such a system cannot deliver pre-market evaluation of a test.

However, individual states sometimes have requirements which are stricter than the basic CLIA regulations. For instance, the State of New York requires laboratories to submit clinical validity data on new tests. One senior laboratory industry figure said that there is very little difference between the data submission for approval of a homebrew test by New York State and a 510K submission for FDA. Whilst all the major reference laboratories and many of the medium-sized ones are New York State-licensed, it is not compulsory.

At present there is no systematic pre-market evaluation of in-house tests and this has been a concern for many (see reports from Task Force on Genetic Testing and SACGT etc.). Although not as explicit as it might have been, the SACGT was clearly supportive of a greater role for the FDA in this area and at the time of the SACGT's investigations the FDA claimed to have powers to regulate in-house tests, but it later retreated from that position. The situation remains unresolved. As indicated earlier this presents particular problems where a use of a test is strongly indicated with a drug but no FDA-approved kits exists for the test. In the past the FDA has dealt with this by reviewing an in-house test and recommending testing with that test until a kit was developed. For example this occurred for therapeutic drug monitoring for FK506, an immunosuppressant used with transplant patients. However, probably of greater significance is the fact that in recent months the FDA has written letters to companies about their in-house tests. For instance, requesting that Genomic Health meet with them to discuss the regulatory status of their OncoType DX test for breast cancer prognosis.

Opinion is divided about whether these actions represent the beginnings of a move into the in-house test area by the FDA or simply intelligence-gathering. The FDA has expressed concern about taking on the whole in-house testing sector because of the implications for its resources, but it is possible that the tests which it considers high-risk, either because of the novelty of the technology or the impact of the test result on patient care, might be brought under its jurisdiction. If the FDA does use these criteria then many, if not all,

pharmacogenomic tests would be likely to be affected. Were this to happen it would probably begin on a piecemeal basis dealing with individual cases as they arise, but would eventually have to be resolved by a formal guidance document or even a rule akin to the ASR rule. The FDA has also been working on modifying the ASR rule itself using a broadly applied risk-stratification approach.³⁹

Our research suggests that there is now a general expectation that this is likely to be how FDA proceeds in this issue, although the details are far from certain. There is currently no consensus within FDA on how to tackle the issue of in-house tests; compounding this uncertainty is the question of FDA leadership which has changed frequently in recent years and which many believe has influenced the FDA's changing position on the issue of in-house tests.⁴⁰

b) Australia

Australia is currently putting in place a new regulatory framework for IVDs, an initiative in part inspired by a concern about unacceptable variations in the quality of in-house testing for HCV (but also initiated to deal with the burgeoning field of genetic testing). The move to bring in-house tests within the revised devices legislation has been extremely contentious, however, there is now agreement on how this will be done. For low- and moderate-risk tests (Classes I-III) laboratories must register with Therapeutic Goods Administration (TGA) and notify the agency about the tests they make; test validation must meet TGA-endorsed standards, but will be carried out by the National Association of Testing Authorities (NATA) and the National Pathology Accreditation Advisory Council (NPAAC), the bodies responsible for assuring laboratory performance in Australia. Should there be concerns about a test in these lower-risk categories then the TGA will be able to investigate. Class IV tests will be subject to the same standards and processes as apply to test kits.

c) Europe

Like the new Australian regulations, the IVD Directive covers both test kits and in-house tests, but unlike the TGA's model it exempts some in-house tests developed by health institutions. The nature of this exemption has been the subject of considerable debate in the UK, but the current guidance from the Medicines and Healthcare Products Regulatory Agency (MHRA) draws a distinction between hospitals (public and private) which are health institutions and therefore exempt from the Directive, and "free-standing laboratories which provide diagnostic services", which are not exempt; the distinction being drawn on the basis that exemptions are granted for a body "which has as its purpose the care and or promotion of public health."⁴¹

Although the UK has a relatively small private lab sector compared with the USA, there are several private labs (including at least three which offer pharmacogenomic testing). However, whilst at least one lab in the UK has CE marked its tests, the situation in the rest of Europe is

³⁹ Gutman, S quoted in Lusky, K 'FDA puts ASR rule back on the table' *CAP Today*, October 2003 They have been working on this for several years but there has been little progress.

⁴⁰ At the request of the SACGHS FDA has also been considering action against some companies which are marketing in-house genetic tests direct-to-consumer[0].

⁴¹ MHRA Guidance In-house IVDs 2004

<http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/0/A93D14B5548D628E80256EE000534595?OPEN>

less clear, although it would appear from discussions with European biotech companies that, at least in some member states, there is no regulation of in-house tests under the Directive. It is understood that this regulatory issue is currently being considered by the European Commission as part of a broader review of the implications of genetic testing for the IVD Directive.

Non-statutory control

As noted above there are other mechanisms to deal with the evaluation of in-house testing, for instance the Australian system already had an alternative system of control through reimbursement – all new genetic tests must be individually assessed by the Medical Services Advisory Council before they can be approved for Medicare reimbursement. However, this system does not cover the private sector.

The UK, like Australia, has a non-statutory system of control. National Health Service (NHS) services and interventions are commissioned by health authorities, and genetic tests are no exception. A system exists whereby only tests approved by the UK Genetic Testing Network (UKGTN) may be funded through such mechanisms. Genetic labs (mainly within NHS hospitals) must join the UKGTN and submit their new tests for evaluation before they are made available to the service. It is also possible for private sector laboratories to join and one has done so, but no tests developed by private sector laboratories have yet been formally evaluated by the UKGTN. The focus of the UKGTN is on tests for inherited disorders.

International harmonisation

Global Harmonisation Task Force

Somewhat equivalent to the ICH in pharmaceuticals, the GHTF brings together a number of countries committed to exploring harmonisation of medical device regulation. Although the work of the GHTF touches on a number of issues relevant to pharmacogenomic testing outlined above, such as clinical evaluation and risk classification, the issues of pharmacogenomics is not being addressed specifically.

OECD

The OECD is undertaking a range of policy work around innovative health technologies. As part of this programme they recently held a two-day workshop on pharmacogenomics. Regulators interacted with industry, clinicians, academic scientists, healthcare policymakers and other stakeholders in a discussion about how to the promise of pharmacogenomics and the policy challenges arising from this new technology. The conclusions of the meeting will be outlined in a policy report (due for publication this year) which will be directed to government and relevant stakeholders.

The OECD may initiate further policy work in this area, as part of its biotechnology programme. It has already spent some years developing guidelines for quality assurance in molecular genetic testing for clinical purposes. These draft guidelines set out to ensure minimum international requirements for quality assurance systems and laboratory practices, facilitate mutual recognition of national QA frameworks, strengthen international co-

operation and increase public confidence in the governance of testing. The guidelines illustrate the potential role OECD can play in developing standards internationally.

Analysis

There has been broad agreement across a range of task forces and committees which have investigated the regulation of genetic testing that tests should not enter routine clinical practice without proper evaluation.

There are two levels of clinical claim that might be made for a pharmacogenomic device, one is the general one such as: “CYP450 genes play a role in drug metabolism.” The second is drug specific, that these particular genes in the case of this particular drug are likely to have this specific effect. Should manufacturers of CYP450 tests be required to submit data for each particular indicated use, or should there be some more general requirement? Is it enough that the genotype/phenotype data appear on the drug label? What about examples like Warfarin where an additional gene (VKORC1) is involved?

There is no formal pre-market evaluation for in-house tests in certain countries and where a process does exist (as in Europe) it is not clear how it is being used.

Furthermore, there are also issues of transparency and information provision - even where there is pre-market evaluation of in-house tests, there is currently no regulatory equivalent of a label for a diagnostic test. The concept of truth in labelling - that those offering a test should be honest about the test’s performance, its strengths and its limitations – does not apply, although of course many public and commercial labs work hard to ensure that those seeking testing are adequately informed. Although laboratory regulation does cover the interpretation of test results and the communication of that to doctors/patients this is at the post-test stage, whereas the pre-test stage, where doctors and their patients are deciding whether to use a test, is not addressed. Furthermore there is no statutory regulation of what types of data should be in a test results report – although this is addressed in professional guidelines.

5 Industry perspectives

Any discussion of industry views must take into account the highly heterogeneous nature of the pharmaceutical and diagnostic industries - not only are these two sectors radically different but each contain a wildly diverse range of companies, from large multinational firms to small and medium-sized enterprises (the latter particularly in the biotech and diagnostics sectors).

The variety of business strategies, products and services is an important factor to take into account; the two sectors include pharmaceutical companies with major diagnostics operations, such as Roche, Johnson and Johnson and Bayer; biotech companies who are both drug developers and laboratory service providers, such as Genzyme; and companies who provide screening services to pharma but also perform testing for use in clinical decision-making such as LabCorp.

Understandably then, there is a diversity of opinions and positions, with some companies having taken positions as strong advocates for the field of pharmacogenomics and others adopting a more cautious attitude. Whilst most commentators agree that pharmacogenomics will not revolutionise healthcare in the next ten years, there is considerable difference in emphasis when it comes to prediction of its likely impact in that period.

The diagnostics and pharmaceuticals sectors face some common challenges, chief amongst them being the validation of novel biomarkers, but there are fundamental differences between them, from which arise some key disagreements on the development of pharmacogenomics.

Pharmaceutical companies

The pharmaceutical industry is now broadly committed to an increasing use of pharmacogenomics in the drug discovery and development process. There is also a growing interest in the more innovative techniques of proteomics and metabolomics in the preclinical phase. Companies which offer genomic screening services to pharma have reported a strong growth in demand in recent years for all phases of drug development and a notable increase in its use in Phase III and this has gained in intensity since the FDA issued its guidance on pharmacogenomic data submissions.⁴²

“The FDA guidance has helped us understand what data we should be gathering. Now in all Phase I trials we get authorisation to gather tissue and do genetic tests.”⁴³

However, the FDA's activities are not the only factors driving the adoption of pharmacogenomics. The commercial pressures of the diminishing pipeline, increasing R&D costs and the unacceptably high failure rate at Phase III where the greatest investment has

⁴² Michael Murphy, Gentrif quoted in 'Pursuing a common goal' IVD Technology Jan/Feb 2006

⁴³ Industry figure, interview

been made are all contributing to this trend. Heightened concerns about drug safety in the wake of high-profile market withdrawals are also playing a role.

Yet many industry representatives still talk about the need to incentivise pharma companies to adopt pharmacogenomics, suggesting that a certain reluctance persists. The degree of commitment varies both across and within companies. A variety of strategies have been adopted: for some companies, like GlaxoSmithKline, pharmacogenomics is now fundamental to their development process; in others, adoption has been more cautious, assessing their use of pharmacogenomics on a case-by-case basis. Concern is expressed by some commentators that there is still a reluctance on the part of marketing staff in pharma companies to accept pharmacogenomics, a fear of letting go of the blockbuster model. One person we spoke to who works for a company providing gene screening services suggested that in some big pharma companies, the use of pharmacogenomics is being driven by marketing departments whose priority is screening out anything that is not pharmacogenomically 'clean'. Another interviewee in a company providing the same kind of service did not see this strategy, but suggested that the companies who are taking a leading role are being led more by their scientists, whereas those who are adopting pharmacogenomics more slowly are led more by their marketing departments.

“There is an embedded infrastructure based on mass-marketing and off-label use, Sales staff see segmentation as a constraint on getting their bonuses which are based on world-wide sales; their incentives have not been re-engineered.”

Reference lab director

However, others suggest that marketing departments are now understanding the value of pharmacogenomics to give their companies competitive advantage. There are other organisational challenges for companies too, just as regulatory agencies need to bring their drugs and diagnostics divisions together so does industry. Many companies are struggling to achieve this.

What can be done to encourage uptake? One suggestion is that there needs to be demonstration projects which illustrate the value and feasibility of pharmacogenomics. At the recent NCI meeting on biomarker development a proof-of-concept study to evaluate biomarkers using an established drug was proposed. Such an experiment would help to lay out the path to biomarker development; provide valuable lessons about the business model for such work and, if the findings were of major impact, could act to galvanise industry.

“The field needs some success stories – this is not an industry of innovators, this is an industry which follows successful models.”⁴⁴

⁴⁴ Pharma industry representative at National Cancer Policy Forum workshop on biomarker development, Washington DC, March 2006

Response to regulators

There is a general view that FDA is the leading agency in this field, that they are far more enthusiastic about pharmacogenomics than other agencies and that this is reflected in the range of guidance documents published, the extensive consultations with industry, the internal reorganisations at the Agency, as well as its regulatory decisions. Attitudes to this leadership role are mixed; overall there seems to be broad support for the FDA's activities but some industry figures suggest that it has been premature, that the FDA is 'getting ahead of the science'.

There is much enthusiasm for the VGDS process with the view that the ability to discuss the use of novel technologies in an exploratory framework has greatly increased their uptake across industry. The general trend towards a more informal approach with companies able to talk to the FDA outside the formal regulatory process is also welcomed, in both the pharmaceutical sector and the diagnostics sector.

Industry has been keen to promote international harmonisation, for instance the PhRMA response to consultation on the FDA's draft guidance on pharmacogenomic data submissions suggested that the FDA guidelines could become a model for other regulatory agencies and that FDA should initiate discussions with Canada, the European Union and Japan.

Technical hurdles and commercial considerations

A recent industry presentation highlighted the following challenges in prospective trials for the discovery and validation of biomarkers:

- Patients enrolment is prohibitive
- Collections of samples is difficult – many are lost to either consent issues or more often due to problems at the RNA quality control stage
- Subject populations tend to be too limited to achieve statistical significance
- Study design tends to be for the drug approval not biomarker discovery – Phase 1-3 paradigm for drug safety-efficacy may be ill-suited to biomarker discovery.⁴⁵

As outlined earlier the commercial promise of pharmacogenomics is that it will reduce the size, time and cost of drug trials. Yet the technical problems outlined above clearly demonstrate that these goals will not necessarily be met. Industry's concern is that using biomarkers will make the development process longer, more complex and more expensive; increasing the risks of drug development with no certainty of benefit.

There is a growing amount of collaboration between the diagnostics and pharmaceutical sectors. Pharma companies are beginning to appreciate that they have to involve diagnostics companies (or their own diagnostics divisions) early on in the drug development process, not bring them in at the last moment when they think they have a worthwhile biomarker. However, even in companies which have a drugs division and a diagnostics division, it can be difficult to foster collaboration and diagnostics companies expressed some criticism of

⁴⁵ Lieven Stuyver, Virco BVBA at DIA EuroMeeting, Paris 2006

pharmaceutical companies whom they consider (like drugs regulators) to be naïve about biomarker development. The relationship between the two sectors is problematic largely due to the very different business models.

Diagnostics

One of the main differences between the two sectors is that in the diagnostics industry intellectual property is much weaker, tending to be in testing platforms rather than content. So competitor products are on the market much faster, usually within two years, giving companies 18 months at most to recoup their R&D investment. Some companies specialise in being ‘fast followers’, the first on to the market with a ‘me too’ test; the problem is summed up in the industry maxim “It’s hard to be first.” Another major difference, related to the weak IP and competitive marketplace, is that profit margins are far lower than the pharmaceutical sector and this is compounded by some significant problems with reimbursement. Furthermore, test kit manufacturers work in a market where they may be competing with laboratories who use their own in-house developed tests which, in most countries, are regulated in a completely different system to the manufacturers.

Finally, whilst many diagnostics companies express concern about these issues and highlight the difficulties they face, their industry is relatively lightly regulated compared with pharmaceuticals and there are advantages to the business model. Thus one biotech company, Celera, has recently decided to focus on diagnostics at the expense of its drug discovery programme, and commenting on the decision its CEO, Tony White said:

“Clearly, if you’ve reduced your burn rate very substantially, if your principal product line and business is now diagnostics—which has lower risk and shorter development times—one can conclude that the pathway to profitability is not only a good bit safer, but also faster.”⁴⁶

Given the differences between the two sectors it is unsurprising that they have different views on the regulation of pharmacogenomics. Perhaps the strongest difference we encountered was the view from the diagnostics sector that the FDA needs to do far more work on the relabelling of already approved drugs. One senior diagnostics industry figure went so far as to suggest that the Agency needs to completely reprioritise its work in pharmacogenomics; that the current focus on new drug submissions was wrong and that its first priority should be a systematic review of all drugs approved in the last 10-20 years to see if their safety and/or efficacy might be improved through the use of pharmacogenomic tests. Another interviewee from the diagnostics sector suggested that the current ad-hoc relabelling process might suit the interests of pharma companies, who are still concerned about losing markets as a result of population stratification, but it was not helpful to diagnostic companies trying to create a market for pharmacogenomic testing.

⁴⁶ Celera makes bold move into diagnostics *IVD Technology*, April 2006

Laboratory professionals have complained that the information on relabelling is insufficient to guide dosing decisions; that it is difficult to find guidance in this area, and that in the absence of clear guidance on which to act they are placed in an uncomfortable position as regards liability. Lack of clear guidance would thus appear to be a significant obstacle to uptake of pharmacogenomic tests.⁴⁷

Such views are part of a general perception on the part of the diagnostics sector that regulatory activities around pharmacogenomics are more geared to the pharmaceutical sector than they are to their industry; that the driving force of activity in this area tends to be the drugs side of regulatory agencies (generally larger and more powerful than their diagnostic counterparts) and that in important respects there is a failure to understand or address the diagnostics sector. As noted in a previous chapter one diagnostics companies heavily involved in pharmacogenomics believes that the FDA's Voluntary Genomic Data Submissions process is 'just for Pharma', a misunderstanding indicative of a significant communication gap. Another frequently cited problem is the FDA's drug-test co-development paper which posits an ideal model of development in which a finished test kit is ready at the same time the drug is submitted for approval. This model, it is suggested by many, fails to take into account the time it takes to move from having the clinical evidence from drug trials that a biomarker is worth using as a co-developed test to actually constructing a robust test kit that will gain regulatory approval.

“The concept paper talked about a candidate marker in Phase I or 2 but this happens rarely - it is more likely to be at end of Phase II or in Phase 3 or even post-approval. It becomes a real problem if the test is mandatory for drug use – it is only a case of some advantage to test, then it is not such an issue to wait until after drug approval to get the test approved.”

Laboratory executive

Another criticism is that lab-developed tests do not feature in the regulatory guidance despite the fact that they are the source of most innovation in this field. Whilst diagnostics manufacturers are concerned about the lack of a level regulatory playing field between laboratory in-house tests and the diagnostic kits they sell to labs, there is also an acceptance of the important role that in-house tests can play as a bridge to manufactured kits. Affymetrix, who are building their own CLIA-certified laboratory, have proposed that FDA guidance on co-development should acknowledge that a validated in-house test may be ready well before a test kit and should be accepted as a valid alternative whilst a kit is being developed.⁴⁸

For industry there is the question of moving from providing an ASR to providing a full-blown diagnostic kit. It has been suggested that the rate of uptake is no faster for a kit than for an ASR so there is no pay-off for going through the more costly and time-consuming approval process.⁴⁹ Industry suggests that currently most pharmacogenomic testing is homebrew.

⁴⁷ See for instance comments of Debra Leonard at SACGHS, March 2006

⁴⁸ Rob Lipshutz at National Cancer Policy Forum workshop on biomarker development, Washington DC, March 2006

⁴⁹ Amy Brower, Third Wave Technologies Presentation at DIA Europe February 2006

The diagnostics industry representatives welcomed the new guidance on pharmacogenetic tests issued by FDA in 2006, in particular the statement that it was expected that most pharmacogenomic tests might be designated as Class II and reviewed by the 510k process rather than the more burdensome PMA. One of industry's main concerns about previous multiplex guidance document was that it was too broad in scope, covering a number of technologies which are quite different. This concern has been addressed to some extent by separating out multiplex tests for a future guidance document.

However, there is still some concern that aspects of the new guidance are rather conservative and do not take into account the novel nature of the technology, for instance, in its approach to establishing cut-off points. This relates to a broader criticism of the FDA's pharmacogenomics guidance: whilst the leading figures at the Agency seem committed to the transformative potential of pharmacogenomics, this attitude is not reflected in guidance which often takes a conservative approach to issues like clinical trial design.

More generally, there is a tension between companies wanting regulatory clarity; to know in advance the standards and processes, and the fact that the regulatory process is iterative and driven by experience with actual submissions. Furthermore companies want on the one hand the simplicity and certainty of a clear regulatory framework, but on the other hand, want sufficient flexibility in the system that not all products are treated in the same way. FDA are encouraging companies to come and talk to them about their new products, but this informal approach does not give the certainty that companies would like when they are taking strategic business decisions.

Whilst for drug companies the hope is that pharmacogenomics will reduce the cost of clinical trials, for the diagnostics sector the reverse may be true. First of all there is a concern that regulators on the drugs side of agencies may have unrealistic expectations about the size and scale of clinical evaluation for new diagnostics – for instance one industry figure quoted a senior FDA official on the drugs side who has suggested that they would want to see two independent randomised clinical trials for a new pharmacogenomic test, a requirement that has never been made previously for diagnostics. Secondly, there is the fact that the combination of highly novel and sophisticated testing platforms, the complex nature of the molecular biology being investigated and the fact that pharmacogenomic tests have a pivotal role in patient treatment, all these factors mean that the level of research and development required is often quite extensive, for instance the leukaemia test currently under development by Roche using their Amplichip platform, is being validated in trials which will involve 6,000 patients before the company takes the test to FDA.

What unites the two sectors is a concern about the lack of standards for biomarker validation. There is confusion over what constitutes an effective test, and there is no systematic mechanism to determine this. In pharmaceuticals there are general benchmarks of being able to outperform a placebo or an active comparator, and diagnostic test development is straightforward where there is a gold standard to demonstrate performance against: where there is no gold standard it is more difficult. It is not clear what the clinical data standards are – how much evidence do you need to demonstrate linkage between the genotype and the phenotype? What are the standards for clinical data, the design issues for clinical trials of

devices, the end points and the powers of calculation required? These issues are also of concern to regulators and to HTA officials.

This is a particularly acute problem in Europe where the IVD Directive is causing problems for manufacturers because it is so vague and much of the responsibility for deciding what is required is placed on the manufacturers themselves. It is far less clear than the FDA system in the US. The IVD Directive does not have thresholds, they are generated by standards or in the common technical specifications. If clinical validation is to be improved then there needs to be clear criteria which test developers can use as a benchmark.

At one of our workshops an industry participant predicted a paradigm shift, suggesting that the beginning of a new era of personalised medicine, with a greater role for diagnostics, would bring both greater reimbursement and higher standards for evaluation.

“If we believe the era of personalized medicine is coming, and these complex tests are going to be a major impact on whether it arrives or not, then ... the paradigm is going to shift from the blockbuster drug to the blockbuster test, and the models that we have right now for drug development will shift to diagnostic test development.”

Focus group participant

However, another industry spokesperson expressed scepticism about whether diagnostics would ever be reimbursed in the same way as pharmaceuticals and then in the absence of better reimbursement the necessary financial incentive to raise standards of clinical data will be missing.

“Diagnostics is almost price fixed, because the reimbursement sets the price ... I don't know how you can get the blockbuster standards when nobody is going to pay blockbuster prices.”

Focus group participant

As noted earlier the diagnostics industry is very concerned that its profit margins are much lower than pharmaceuticals and that demands for greater clinical data will be unreasonable in light of expected remuneration.

One important concern is whether the regulator will require data on clinical utility. Some industry representatives argue that placing a heavy burden of clinical utility data on diagnostic tests is unrealistic, it was argued, because tests are intermediate outcomes; their impact on patient management varies depending on the physician's treatment options. Thus, they say, demands for greater evidence should focus on clinical validity rather than clinical utility unless the manufacturer makes clinical utility claims.

The diagnostics industry is as much concerned about the issue of reimbursement as it is about statutory regulation. One possibility is a closer linkage between market approval and

reimbursement and one way to achieve that would be for companies to involve reimbursers in the early stages of stage of test development so that both the regulator and reimbursers can comment on whether the proposed studies will be acceptable. Another recurrent policy proposal from industry was the idea of value-based reimbursement, that organisations which add value to the healthcare system should, in some way, be recompensed for that through improved reimbursement. The greater demands of the reimbursement system – for firm evidence of clinical utility of new tests – should be matched by a level of reimbursement which reflects the clinical value they have been shown to provide.

6 Conclusion

In analysing the regulatory activities we have set out here it may be helpful to return to our model of the practice of regulation as encompassing three broad areas of activity: information-gathering; standard setting and behaviour modification. Clearly regulators have been active in all three areas when it comes to pharmacogenomics. There has been a very broad process of public consultation, primarily with industry but also with other stakeholders, on a wide range of issues. This consultation has allowed the regulatory agencies to gather intelligence about how drug companies are using genomic data and, through the creation of mechanisms for voluntary genomic data submissions regulators have been able to educate themselves about the use of such data. The publication of a range of concept papers and guidance documents has also helped to clarify the regulatory agencies' expectations for quality and types of data they require and the submission processes. Standard setting has also been initiated through the approval of individual products (and through relabelling of existing products), a process which sets benchmarks for future regulatory submissions.

Finally, all this activity, from the extensive public consultation, the issuing of guidances and the approval of individual products is all designed with the goal of behaviour modification. The regulatory agencies' goal being to increase the use of pharmacogenomic data, as part of a new understanding of the underlying biological mechanisms of disease and drug response, in the development of safer and more effective therapies.

So how effective has this activity been? Objective measures might include the number of new drug submissions including pharmacogenomic data; the growing use of pharmacogenomics in all phases of drug development; the growth in the number of pharmacogenomic tests for new and existing drugs; the number of existing drugs which have been relabeled to include pharmacogenomic data. Subjective measures would be the attitudes and opinions of industry such as we have tried to capture in the previous chapter. Regulators are also subject to peer review from within and without their own agencies.

There is a general consensus that FDA have led the way in this field. Leadership is of course a mixed blessing, leaving one open to both praise and criticism. One criticism which is repeatedly heard stems from the perception that this field is moving more slowly than many anticipated, that the impact of pharmacogenomics in healthcare has been far less than was promised in the heady excitement of the Human Genome Project. In the light of this lack of progress some consider it premature to be attempting to reshape drug development and approval as an enterprise founded on pharmacogenomics. There is a sense in which a regulator's main pre-occupation must of necessity be to deal with the here-and-now, the daily grind of new approvals. As we have seen there is a concern that guidance may be getting ahead of the science.

The fact that other regulatory agencies have not been as active as FDA is not necessarily a sign of lesser commitment. The US regulator has far greater resources to bring to bear on this field than any other; to compare for instance FDA and EMEA - FDA have 20 full-time staff in the IPRG whereas EMEA have none in their equivalent PWG. Regulators in other agencies have other pressing priorities to deal with in the emerging technologies field including gene

therapy and stem cell therapy. Despite their lack of resources, the other agencies are also playing an active role – for instance in the clarification of terminology, an important area for an emerging technology.

A major difference between US and other countries has been the FDA's commitment to relabelling. Whilst their recommendations in relabelling have been relatively cautious their enthusiasm for approving relabelling is far greater than other agencies (the recent decision on Irinotecan/UGT1A1 being a prime example). In this respect they are clearly less cautious than their regulatory peers. Individual differences in specific regulatory approvals are of course inevitable, but there is a view that there is an underlying strategic difference here. The FDA have embraced relabelling as a valuable mechanism for encouraging the adoption of pharmacogenomics by both pharma and diagnostics and, not least, for educating clinicians in the complexities of using such data in therapeutic decision-making. As we have seen there has been criticism of their activity in this area. The Agency is caught between wishing to encourage pharmacogenomics but needing to ensure they do not get ahead of the science - should they make weak recommendations which do not give clear guidance? Are there educational initiatives which could make the basis for decisions easier or is it simply a case of providing more data on the label?

The call from senior lab directors for clearer pharmacogenomic labelling, illustrates the point that regulators must ensure that they are working with the diagnostics sector as well as the pharmaceuticals sector. There seems to be broad international agreement regarding the risk classification of pharmacogenomic tests; that whilst they may not pose the seriousness of risk of tests used in blood screening, they are nevertheless relatively high-risk devices requiring thorough pre-market evaluation. The notable exception to this agreement is Europe, where they are by default low-risk devices. It will be interesting to see how this issue is dealt with in the consensus-based work of the GHTF, where work is currently underway on classification. Participants have indicated that in this forum European officials have acknowledged the limitations of their current system for risk classification. In the meantime, as things currently stand there is nothing to stop a company self-certifying its pharmacogenomic tests and bringing them onto the European market without any pre-market evaluation. But, that said, it is in the power of any individual member state to apply special controls to pharmacogenomic tests and/or to apply for their inclusion (either as a class or on a case-by-case basis) in Annex II List B.

Notwithstanding these differences in approach one of the most notable features of the emergence of pharmacogenomics in the regulation of pharmaceuticals is the commitment to achieving international harmonisation. Whilst the well-established work of the ICH means that such harmonisation is not in itself novel, the attempt to create harmonisation *ex novo* is unusual. Although moving at different speeds and with different priorities and problems, the leading ICH nations - US, Europe and Japan - are strongly committed to this goal. It remains to be seen whether those who wish to move fastest can do so in a way which does not preclude a consensus-based approach.

It is notable that there is no comparable movement for international harmonisation in the IVD devices sector. The GHTF has not addressed the question of pharmacogenomics and there is no indication that it will do so. This is indicative of the degree to which the impetus

for change is coming from those involved in drugs regulation rather than those on the devices side. However, the OECD guidelines for molecular genetic testing suggest that in the area of in-house testing and the delivery of tests through laboratories there is the potential for international harmonisation.

Regulators and health policy makers must think carefully about what can be achieved by different control mechanisms, about the levels of evidence required at licensing, at reimbursement and for the development of clinical practice guidelines. They must think also about the resources required to generate pharmacogenomic knowledge, for instance, is there sufficient public expertise to support the regulatory process? Our previous research suggested that there was an urgent funding need for development of this expertise.

Although the adoption of pharmacogenomics in the drug development process has been gradual, it is now affecting every stage – from Phase I to Phase IV. It is a two-way process with regulators having to adjust their systems to take into account the new technologies being adopted by industry and with the regulatory agencies influencing the adoption of pharmacogenomics through the development of new guidance documents. It is possible to envisage that in the future, particularly in the context of a greater emphasis on safety data, all new drugs will require a pharmacogenomic section included in their approval submissions but for some time to come such data is likely to be mandatory only in certain circumstances. The most difficult decision which regulators face is around this issue: would mandatory data requirements be the most effective way to promote pharmacogenomics? Does the state of the science justify such a move and will the technical and commercial hurdles associated with pharmacogenomic research slow down, rather than speed up the pipeline?

“It is always too early to evaluate a new technology, until it is too late”

Focus group participant

Annex I Guidance documents

FDA

- Pharmacogenetic data submissions – final guidance (March 2005)
- Drug interaction studies – study design, data analysis and implications for dosing and labelling (October 2004)
- Drug-Diagnostic Co-Development - Concept Paper (April 2005)
- Pharmacogenetic tests and genetic tests for heritable markers (February 2006)
- Drug Metabolizing Enzyme Genotyping Systems – Class II special controls guidance (March 2005)

EMA reflection papers

Released

- Terminology in pharmacogenomics
- Draft guidance on briefing meetings
- Concept paper on biobank issues relevant to pharmacogenomics

In preparation

- Pharmacogenetics and Pharmacokinetics Studies
- Guideline on Pharmacogenetics briefing meetings
- Use of genomics in clinical intervention trials to explore interaction between treatment and genomic traits
- Experience on pharmacogenomics in the oncology centralized procedure

Japan

- Submissions of information to regulatory authorities for preparation of guidelines for the use of pharmacogenomics in clinical studies (March, 2005)

Annex 2 Methodology

This report draws on four years of research in the area of pharmacogenomics and clinical genetic testing. In the course of this research we have surveyed both the academic and grey literature and engaged with over 150 individuals through one-to-one interview and small focus groups – talking to opinion leaders in key stakeholder groups – regulators, industry, clinicians, patients groups and health policy-makers. For this report we supplemented our existing knowledge base with a further literature review and with a series of one-to-one interviews, and participated as observers in four meetings at which stakeholders discussed issues relevant to the report. Participation in these meetings facilitated formal interviews, informal discussions and allowed us to observe at first-hand interactions between regulators, industry, clinicians, healthcare policymakers and academic researchers.