
REGULATING PERSONALISED MEDICINES

CMR INTERNATIONAL INSTITUTE WORKSHOP

14-15 April 2003, Nutfield Priory, UK

SUMMARY REPORT

Margaret Cone and Stuart Walker

SECTION 1. OVERVIEW

If it were not for the great variability among individuals, Medicine might be a science not an art. (Sir William Osler, The Principles and Practice of Medicine 1892)¹

The unravelling of the human genome and advances in genetic research are now opening up new horizons in the understanding of the science behind the 'variability among individuals'. At the forefront of this research is the integration of pharmacogenomics and pharmacogenetics into the discovery and development of new medicines. Such medicines have the potential to be 'personalised' or tailored for optimal efficacy and minimal risk in the individual patient.

The implications of these developments for pharmaceutical research and regulation and the impact on practical and economic aspects of drug development and healthcare delivery were discussed at a Workshop convened by the CMR International Institute for Regulatory Science in April 2003 in Nutfield, Surrey, UK.

It was clear from the discussions that the pharmacogenomic era has begun in earnest and that it is no longer a question of *whether* it will deliver a new generation of medicines, but *when*.

A concern that was re-iterated throughout the workshop was that, whilst pharmacogenomic research must be conducted within an appropriate regulatory framework, premature and inappropriate additional regulation could hamper development of the science. Dialogue between industry and regulators and a willingness to share experience of the issues is critical to moving forward.

In many cases pharmacogenomics may be integrated into the development process as one of many tools to improve discovery and increase knowledge of disease aetiology. The 'ultimate' personalised medicine, however, is one that is marketed in combination with a genetic diagnostic test, or with a labelling requirement that such testing be undertaken. This raises many regulatory issues that are yet to be resolved in relation to ensuring the sensitivity and specificity of tests and setting standards for their control.

There are also significant unresolved issues related to the economics of developing medicines for targeted subsets of the patient population rather than the traditional 'one product fits all' approach. There will also be major implications for the 'payers' who will need to be convinced of the cost benefits of medicines which will almost inevitably be higher priced, and will carry the cost of additional diagnostic testing.

There are also practical and economic issues for healthcare delivery infrastructures in moving towards an era where diagnostic genetic testing, as a prerequisite to prescribing medicines, could become the norm, rather than the exception.

By its very nature, personalised medicine will mean greater involvement of patients in decisions about their treatment. A concerted effort is needed to present the new technology in a positive light using language and terminology that can be understood by the lay public.

¹ Quoted in the Workshop presentation by Dr Christopher Chamberlain

Definitions

For the purpose of the Workshop the following definitions¹ were used:

Pharmacogenetics (PGt): is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics (PGx): is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

¹CPMP position paper on terminology in pharmacogenetics, London, 21 November 2002, Reference EMEA/CPMP/3070/01:

Summary Report

This report is presented in three sections:

Section 1: Overview

Section 2: Outcome, summarising the main points and recommendations from the Syndicate discussions

Section 3: Meeting Summary, giving information on the individual presentations and the subsequent questions and answers that they generated.

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science has been set up as a not-for-profit division of the Centre for Medicines Research International Ltd in order to continue its work in the regulatory and policy arena, and to maintain the well established links that the Centre has with regulatory authorities around the world. The Institute operates autonomously, with its own dedicated management, and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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Workshop Organisation

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SECTION 2. OUTCOME

In Session 3 of the Workshop, chaired by Dr Mike Clayman, four Syndicate Groups discussed two topics:

Topic A: *Regulatory factors in the socio-economic and ethical issues raised by clinical trials and marketing of medicines developed on the basis of pharmacogenomic /pharmacogenetic factors.*

- **Syndicate 1:** *Chair: Chris Towler, Imperial College, London;*
Rapporteur: Simon Larkin, Kyowa Hakko UK Ltd
- **Syndicate 2:** *Chair: Gunnar Alvan, Medical Products Agency, Sweden;*
Rapporteur: Samuel Vozech, Swissmedic

Topic B: *Regulatory factors in the R&D process: The pace and procedures for developing regulatory guidance and requirements for the different phases of development of medicines that are designed around pharmacogenomic/pharmacogenetic factors.*

- **Syndicate 3:** *Chair: Stuart Walker, CMR International;*
Rapporteur: Stewart Geary, Eisai Co. Ltd
- **Syndicate 4:** *Chair: Michael Zuehlsdor, Bayer AG;*
Rapporteur: George Butler, AstraZeneca Pharmaceuticals

Each group was asked to identify two 'action items' as well as providing general discussion points from their deliberations. Items from the Rapporteurs' reports and the recommendations from the Syndicates are summarised here.

POINTS FROM THE DISCUSSION

Avoiding premature regulation: The concern is less about the changes in actual regulations (which would take years) and more about rushing into guidelines and guidance documents at too early a stage. This is not just an issue between regulators and industry, but can also be the result of action by advocacy groups which are already having an impact in this field. Among the areas of issues are:

- the influence of patent law;
- privacy regulations;
- controversy over the issues of general genetic screening and how this impacts the acceptance by ethics committees of pharmacogenetics in drug development.

Of particular concern is the fact that ethics committees will be providing guidance but such guidance will not necessarily be consistent from one case to the next.

Case-by-case approach: Recommendations and decisions made on a case-by-case basis are the only feasible approach for a science in its infancy but the question arises of how long this can be sustained. Current discussions of the issues are closely related to individual cases and an assessment of:

- Safety vs. efficacy issues;
- An absolute vs. a relative need for a pharmacogenetic test;
- The predictive value of the tests;
- The risk vs. the benefit of performing or not performing the tests.

Regulators were, however, concerned about how in the absence of agreed guidance, they would deal with applications that are heavily dependent on pharmacogenomic data which may be received in the near future.

Future implications for existing products: A case might arise where the registration of a new product introduces significant new pharmacogenomic factors that may impact on other authorised products in the same therapeutic field. Would this lead to a re-evaluation of the current products?

The ethical dilemmas are not new: Although important safeguards must be imposed when obtaining and handling genetic information about individuals these do not raise any significant new ethical issues. Sensitive health-related and financial information on individuals is already handled within existing privacy and human rights laws as well as ethical codes and confidentiality agreements.

Public perception of genetics: There is a different *gravitas* attached to genetic information because of the concern that it provides information about factors that do not necessarily affect the individual now, but may have an effect on health and the ability to function in society, in the future. Furthermore results of genetic tests may also have implications for relatives in cases where heredity is a factor. Sensitivities may be linked to a general distrust of scientists, politicians and industry and fears that the information may be misused.

The medical model is changing: There is already a change in emphasis from 'population health' to personalised health with the public actively seeking information, often from the Internet, on health, diseases and medicines.

The generation factor: It was suggested that concerns about genetic testing may only be a problem for the 'in between' generation coming to terms with a new technology – in the way that there was resistance to the invasion of computers into everyday life. The next generation might accept, as normal, that a DNA swab should be taken from a newborn baby and stored in a database.

CIOMS work in this field: It was noted that a CIOMS working party is preparing a report, expected at the end of 2003, which will address ethical, regulatory and cost issues.

Interaction between pharmaceutical and diagnostic producers: A significant 'gap' was identified in communication between regulatory authorities and between companies involved with pharmaceuticals and with *in vitro* diagnostics (IVDs). Firstly there are harmonisation initiatives on guidance and regulation of medical devices and IVDs, through the Global Harmonization Task Force (GHTF) but the discussions do not involve those involved with pharmaceutical products that might be affected. Secondly, there could be significant regulatory and commercial consequences if IVD manufacturers start creating markets for new tests, that define populations that should or should not be taking medicines that are already on the market.

Academic involvement: There was concern about a lack of academic infrastructure to bridge the gap between basic research on genetics and the practical application of pharmacogenetics. Similarly there appears to be a missing link between clinical pharmacology and genetic epidemiology. Although academic interest may increase once more pharmacogenetic-based treatments become available, there is currently a perceived lack of opinion leaders and academic forums that can offer independent scientific advice.

Educating pharmacists and physicians: There is a potential gap in the infrastructure that will be required for performing the new tests and interpreting the data. This may involve new roles for the pharmacist, and both pharmacists and physicians will need education in understanding the tests and counselling patients. It was noted that issues raised by pharmacogenetic tests may be broader than just the use of medicines and may be relevant to the patient's lifestyle or other medical problems.

Test validation: There needs to be discussion on the amount and type of work required to validate pharmacogenetic tests, with a distinction made between those tests carried out for the development of new products and those that are carried through to the market place for routine use with an approved medicinal product.

Research vs. clinical care: Situations could arise where future research reveals a matter which is of significant medical importance to clinical trial patients whose results are on record from earlier trials. If data has not been anonymised, does the company have an ethical obligation to follow-up the patients? One view was that there was a danger of confusing research and clinical care. Participation in a clinical trial or in the research has defined boundaries that are agreed with the patient on day one and should not include retrospective examination of data in the face of new information and feedback on their clinical condition. There was not, however, unanimity on the subject which was recognised as an important one which could 'be the beginning of a separate Workshop'.

EUDRAGENE: Whilst discussing the need for information exchange between health authorities, academia and industry the subject had been raised of the EUDRAGENE project, currently being developed by the London School of Hygiene, with funding from the EU. The objective set up a database linking reports of adverse reactions involving marketed drugs with information from DNA samples. The intention is to involve pharmacovigilance centres and academic networks throughout the EU. The project would be set up on the basis that there will be free (suitably anonymised) access to the data but those using the database are obliged to feed back the results of their investigations and studies. A publication process will safeguard intellectual property and ensure that the data cannot be exploited for purely commercial purposes. The EU grant is to set up the framework for the project but additional funding will be needed to support the collection and testing of DNA samples.

Prospective safety: There are analogies between the safety and efficacy data required for orphan diseases (the 500 patient dossier) for which guidance already exists and the requirements for small patient populations defined by pharmacogenetic parameters. Separate guidance on this is not required. The sequential development of such products to include broader indications could be seen as a 'back door' to achieving a blockbuster in some cases, for example in oncology and anti-infectives, and raises other issues, particularly of safety. It would be expected that health authorities would need a large study including 'all comers' in to provide assurances on safety, beyond the smaller indication.

EU Briefing meetings: Participants had welcomed information on the informal briefing meetings to be held between the CPMP Working party and industry² but were concerned that only three such meetings per year were planned. There was a need for more opportunities for the subject to be discussed with EU regulators in an open way, but with no commitment, and it was hoped that other opportunities for such interactions would be provided.

Economics of drug development: A comparison was made between the investment costs and returns for the current blockbuster drugs and medicines for smaller, targeted populations. It was apparent that the development of medicines for smaller markets is only economically viable if the new technologies result in lower R&D costs and/or a shorter development time. In the short term, there were doubts that either would be achieved. The worst case scenario is where development costs and times remain as at present but the market is considerably reduced. On a more positive note it was pointed out that some so-called blockbuster drugs are only used in a relatively small proportion of the totality of patients suffering from a widespread disease and a targeted medicine could therefore have the same economic profile as a conventional blockbuster. For less prevalent conditions,

² EMEA/CPMP/4445/03 Concept Paper on Pharmacogenetics 'Briefing Meetings', 24 March 2003

however, the economic equation could only be balanced if higher prices could be negotiated on grounds of improved efficacy and safety leading to greater cost efficiency.

Change in environment: A 'must' for bringing about a revolution in the way medicines are developed and administered is a change in the general environment for medical treatment. This includes a change in the public perception of risks of medicines, a better understanding of their value and, in relation to the physician an acknowledgement of the problems associated with off label use.

Creation of inequalities: To achieve the scenario where personalised and targeted medicines become the norm rather than the exception, significant changes and improvements will be needed in the healthcare infrastructure. In the interim, there will inevitably be an increased gap, not only between the industrialised and developing world, but also within industrialised countries where the infrastructure is likely to be available in specialised centres and not to the general practitioner.

Inequalities can also be expected by the creation of 'pharmacogenetic minorities' for whom the development of medicines is not economically viable.

RECOMMENDATIONS

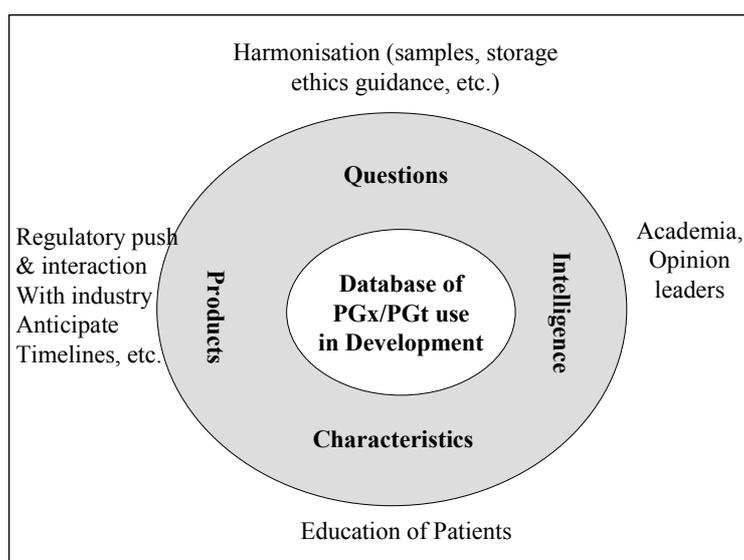
Database of pharmacogeonomics technology used in product development.

A prospective database should be established that would:

- look at the impact of pharmacogenomic techniques on drug development and on the timelines of drug development;
- be a mechanism for sharing experience and learning from case studies on the application of these techniques;
- help to inform regulators about the products in the pipeline for the next 2-5 years
- stimulate interest from opinion leaders and call the academic attention to pharmacogenetic testing issues;
- form the basis for state-of-the-art papers on the use of this technology.

A diagrammatic representation was presented of the interaction between industry, regulators and other interested parties, that might be stimulated by such a database (figure 1).

Figure 1



Harmonisation of procedures for sample collection, storage and future analysis

A forum is needed for the discussion of issues related to:

- Confidentiality of collected samples and anomomysation and decoding including:

- whether it is better to anonymise or use some form of coding method for handling samples that are stored;
- differences in practices between different countries;
- the need to address the concerns of ethics committees.
- Sample storage and the ability to carry out future analyses on stored samples:
 - whether this is covered implicitly in patient consent;
 - if not, how to obtain explicit consent to all pharmacogenetic tests that the company may wish to perform at a later stage.

As a background to such a forum there would need to be a review of existing regulations by region.

Development of ‘good gene practice’

Whilst specific regulatory guidance for the development of medicines may be premature, there is a need to develop a ‘regulatory framework’ for establishing good practices in the field of genetic testing. An example is that tests should only be carried out that are clearly linked to clinical utility. This is becoming particularly urgent with genetic tests being offered via the Internet. There is a need to provide information to enable the public to distinguish between products and services that can be trusted and those that fall outside any form of control.

A simplified terminology to facilitate education

There is a need to develop a new, non-threatening vocabulary and simplified terminology to convey to the public and politicians about a new generation of medicines ‘tailored’ to the needs of individuals rather than the general population. In the public mind the terms ‘genes’ and ‘genetics’ have developed negative connotations by association with, for example, the adverse publicity surrounding genetically modified foods, and press stories about human cloning and the spectre of genetic manipulations (‘designer babies’).

A simplified phraseology should explain the role of the new diagnostic tests in terms of:

- Health profiles to determine the best type of therapy for the individual. (This will require adequate assurances about the privacy information on disease susceptibility).
- Treatment guidance to ensure the best effectiveness and safety in the use of a particular medicine in the individual;

Whilst explaining the nature of these tests openly, they should not be portrayed as significantly different from other diagnostic tests on blood and urine samples that are routinely used as guides in diagnosis and the prescription of medicines.

It was also suggested that the term ‘personalised medicine’ should be revisited. This could be perceived as invading personal privacy and jeopardising personal information and it may be preferable to speak in terms of better targeting of therapy.

Counterbalancing the misinformation through education

Education is the key to ‘demystifying’ the nature of pharmacogenomics, but the public is currently obtaining information predominantly from the media where stories may be sensationalised or placed in a negative context. There is a need to redress the balance through positive, factual information and balanced arguments. Politicians and policy makers, regulators, industry and scientists all have a role.

Of particular importance is the need to separate the role of genetic testing in relation to the optimal use of pharmaceuticals from its role in susceptibility profiling.

Conditional approvals

Increased implementation of ‘conditional approval’ procedures with specific postmarketing safety surveillance obligations, should be considered for medicines where targeted efficacy studies are appropriate, and a smaller Phase 3 safety database can be justified.

There is a potential 'Catch 22' situation where the drug developer needs to know what will be required by the regulatory authorities for marketing authorisation but they, in turn, will need to see the dossier in order to say what is required. A new form of conditional approval could meet such situations, with the company being given specific responsibilities for safety monitoring. It could be envisaged that an independent body might be established to oversee the collection of pharmacovigilance data for these products.

Patient Information

The standards and requirements for patient information needs to be reviewed for the new generation of products where the patient should participate to a much greater extent in the therapeutic decisions. The point noted above about the need for more appropriate language and terminology is also applicable to patient leaflets and information.

Follow-up Workshop

Two of the Syndicates arrived at the same conclusion, that there should be a further CMR Institute workshop within the next 18 months which should:

- Focus on case studies giving actual (albeit anonymised) examples of technical and regulatory issues that are being encountered;
- Provide further information from the evolving database

RESPONSE FROM THE CMR INSTITUTE

In his closing remarks at the end of the Workshop, Professor Stuart Walker, Executive Director of the CMR International Institute for Regulatory Science welcomed the positive feedback from the Syndicate groups that had prompted the call for a follow-up event to be convened. This recommendation would be taken forward to the Institute's Regulations Advisory Board which would be reviewing the Institute Agenda for 2004.

It was important that the recommendations and discussion points be developed further in terms of the methodology to be employed and the deliverables that might be expected. Professor Walker was confident that the Board would endorse the proposal for a further Workshop, possibly in the US which would allow industry and regulators to revisit this important topic and review the progress that has been made. This is a journey, he said, which is going to take us forward over the next five to ten years to an era which will not only revolutionise the way pharma R&D is carried out but will also significantly affect the nature and range of medicinal products available for patients.

REGULATING PERSONALISED MEDICINES

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SECTION 3. MEETING SUMMARY

SESSION 1. PHARMACOGENETICS AND PHARMACOGENOMICS DURING CLINICAL DEVELOPMENT

Chairman: Dr David Jefferys, Medicines and Health Products Regulatory Agency, UK

Opening the Workshop, Dr Jefferys looked forward to a stimulating and constructive discussion of the use of pharmacogenomics and pharmacogenetics in the drug development process. With estimates that there may be as many as 15,000 new genetic tests marketed over the next five years, two of the objectives of the Workshop were to explore how regulation should be approached in this fast developing field and to look at the ways in which the health services might respond to the consequent changes in medical practice.

Integrating pharmacogenetics and pharmacogenomics into drug development: Perspectives from a global pharmaceutical company

Dr Bob Holland, AstraZeneca

Integrating genetics and genomics into drug discovery is now a reality and, with the declining number of new medicines currently reaching the market, the innovative industry must 'adapt or die'. These were the messages with which Dr Bob Holland opened his presentation. He discussed the ways in which the new technologies can be applied in the drug discovery process and the drivers that influence decisions to follow, or avoid, the path to 'personalised medicines' accompanied by genetic diagnostic tests.

Pharmacogenomic and pharmacogenetic techniques are opening up fascinating new possibilities in drug discovery and development, with the ability to generate information for target identification and target validation and to explain variations in response, adverse events and pharmacokinetics. There is now the realistic prospect that patient populations can be prospectively characterised according to likelihood of response and propensity to adverse reactions. Genotyping of the target is now carried out routinely, although the aim of Discovery is, in fact, generally to avoid truly 'personalised' medicines with unrealistically small patient populations. Rather, the aim is to ensure that the new candidate drug acts on the most frequent allelic variant of the target, and that this variant represents the majority of patients suffering from the disease!

Dr Holland, however, identified two circumstances where the development of targeted, 'personalised' medicines would be the appropriate approach from the outset of a clinical development programme. The first is where there are sufficiently compelling efficacy drivers, for example in serious progressive diseases where a population subgroup can be identified prospectively for whom the product is a clearly superior treatment. The second example is where there are serious adverse reactions for which susceptible individuals can be identified prospectively. In neither case, however, would the strategy be worth pursuing if there were equally useful products on the market without the need for a diagnostic test.

As an alternative, Dr Holland suggested that medicines might end development as targeted therapies even when this was not the original plan, if genetics (and genomics) samples were collected during a conventional programme and the drug turned out to have sufficient efficacy only for a subgroup of patients (who could be identified retrospectively using those samples), or the drug turned out to generate serious adverse reactions in a group of patients (again who could be identified retrospectively).

Dr Holland felt that, after some unrealistically optimistic predictions that genomics and genetics would solve all problems, a degree of 'measured pragmatism' is entering into the discussions. The science should be regarded as another tool for generating information to add to the overall knowledge base for developing new therapies. Pharmacogenomic/genetic

research needs to be undertaken in an environment where the ethical, regulatory and legal issues are clearly understood, and where there are the appropriate consents for access to DNA and tissue samples and correlation with phenotypic data. In his opinion, there was no need to rush into further regulation in this complex field whilst the Industry, health care providers and regulatory authorities are still learning the basics about the kinds of information that should be sought, how it should be sought and validated, and how it should be interpreted.

**Integrating pharmacogenetics and pharmacogenomics into drug development:
Perspectives from a biotechnology company**

Dr Robert Pietrusko, *Millennium Pharmaceuticals*

Using the analogy of the 'perfect storm' Dr Robert Pietrusko suggested that many changes were currently happening which could have a profound effect on healthcare industry dynamics. These include: changes in the structure of the industry; increased patient and consumer involvement and access to information; new communication mechanisms including the Internet; and economic issues of pricing and reimbursement. At the same time exciting advances are being made in genomics, proteomics, imaging technologies, devices and biosensors, and molecular medicine.

Genomics provides an opportunity to define health and diseases in terms of molecular 'fingerprints'. Mechanistic pathways can be defined with important implications for preventive, diagnostic and therapeutic strategies. With the 30,000 genes in the human genome having been unravelled, the major challenge is to identify and validate the 'druggable' targets. At present industry is known to be working on 200-500 such targets but there are many thousands more. Pharmacogenomics holds the potential for predicting and assessing the efficacy and toxicity of drugs and identifying drug responders and non-responders. It may also be the key to addressing the alarming estimates that some 100,000 patients die each year as a result of adverse drug reactions (ADRs).

Since it takes some six years and \$30 million to take a compound to an IND, it is critical to identify key criteria in drug target selection and Dr Pietrusko suggested that these were:

- **Druggability:** Has the target class been used to develop Phase I compounds with success?
- **Assayability:** Is the target class amenable to assay formats compatible with high throughput screening?
- **Disease Hypothesis:** Do the expression data and the protein class point to a disease-relevant pathway?

Dr Pietrusko described the way his company was developing a comprehensive programme to bring together all the research tools to look at druggable targets, including informatics, computational biology, genomic microarrays, databases of patient data and tissue sample information, proteomics, tissue microarrays, immunohistochemistry (IHC), and transgenic knockout animals. Referring to the importance of strategic study design he described the way in which the new technologies are applied to:

- **Early discovery:** establishing a conceptual basis for biomarkers, identifying biomarkers and beginning validation, transcriptional profiling;
- **Preclinical Pharmacology and Toxicology:** establishing the biochemical mechanisms and biomarkers; studying biomarkers in pre-clinical pharmacology and/or toxicology; carrying out a human pilot if appropriate and developing animal models for predictive toxicology;
- **Clinical development:** Subphenotyping the human disease; establishing pharmacodynamic endpoints and surrogate markers and using pharmacogenomics to stratify the disease based on drug response;

- Phase 2B/3 confirmatory development: Bridging biomarkers to a wider population, using pharmacogenetics to study special populations and potential drug interactions.

Looking to the future, Dr Pietrusko asserted that the genomic/proteomic-based drug discovery era has started and that clinical development and commercialisation of new medicines will increasingly be driven by functional genomics, proteomics and targeted therapies. In the specific area of cancer treatment, we can expect predisposition testing to expand and screening tests to improve. He predicted that the concept of personalised medicines would shortly be incorporated into the new drug approval process.

The future 'pendulum' could, he suggested, swing towards a more positive paradigm with enriched trials in focused populations only, less costly development, targeted claims and reduced development timelines. A 'negative' swing would result in efficacy data being required in all patients with the 'general' disease, whilst still requiring pharmacogenomic data and exposure data being required in large populations, with many subset analyses. This would obviously lead to more costly development and prolonged development times.

Integrating pharmacogenetics and pharmacogenomics into drug development:

MHLW Perspective

Mr Daisaku Sato, Ministry of Health, Labor and Welfare, Japan

Mr Sato was unfortunately not able to travel because of the prevailing international situation but kindly provided slides and a paper for the Workshop.

Pharmaceutical companies and genomic researchers in Japan, as in other ICH regions, have turned their attention the role of pharmacogenomics and pharmacogenetics in the cost effective development of new drugs. There are, however, issues to be addressed from a scientific, economic and public health point of view in order to maximise the benefits for the patient.

To date, MHLW has only issued guidance on pharmacogenomics/pharmacogenetics (PGx/PGT) in relation to guidelines on clinical pharmacokinetics and pharmacodynamics (PK/PD). The use of PGx/PGt techniques have been observed in seven PK/PD studies initiated in Japan, but predictions from the Human Science Foundation of Japan indicate that 40% of Japan-based companies are planning PGx/PGt-based clinical trials in the next few years. Governmental and industry initiatives started in 2000 to set up a SNP database aimed at identifying disease-related, and drug-response related, SNPs, such as polymorphism of metabolic enzymes.

In terms of progress in developing personalised medicines, Mr Sato noted that, in common with other countries, the greatest progress appears to be taking place in the field of cancer treatment, both in terms of therapy and avoiding adverse reactions. He observed that this is an area where, due to its life threatening nature recognised genetic mechanisms, genetic testing is likely to be less of an obstacle to patients.

Three issues were of particular concern in the wider application of PGx/PGT during drug development. Firstly, patient selection in clinical trials may lead to greater efficacy but, by reducing the number of patients, the safety database is reduced which may lead to rare adverse drug reactions being overlooked. Secondly was the question of whether and under what circumstances genotyping should be mandatory for the administration of certain medicines, other than in cases where there are serious safety issues. This leads to the third issue of the cost implications of medicines that require additional diagnostic testing and whether this can be covered under existing insurance schemes.

On the question of guidelines, MHLW recognises that PGx/PGt is still at the fact-finding stage and to date there are no plans to develop regulatory guidance in Japan. Mr Sato indicated, however, that a consensus guideline would be required in the near future in order to provide a sound scientific and ethical approach. Experience of ICH had shown that

transparent regulatory guidance would also encourage public acceptance of, and confidence in, the new technologies.

He suggested that such guidance should address:

- terminology and definitions;
- the scientific basis for incorporating PGx/PGT into clinical development and postmarketing studies;
- issues related to patient privacy and the protection of genetic information.

Looking to the future, Mr Sato noted that there were those who believed that further scientific research into PGx/PGt could resolve the issues related to the data required for bridging studies although there is still no scientific consensus on how personal differences relate to population differences.

Points from the discussion

Avoiding ADRs: Dr Bob Holland was asked to expand on how to translate the theoretical ability to avoid adverse drug reactions (ADRs) into clinical reality and whether there are examples where a clinical trial based on pharmacogenomic data has been carried through into the population. Replying, Dr Holland indicated that there were not yet any true examples and that the main experience is in tracking gene markers for susceptibility to different adverse reactions, although this may only be providing confirmation of prior knowledge of likely mechanisms.

In a follow-up question it was noted that hypotheses about adverse reactions could obviously not be tested by taking populations at high specified risk. On the contrary, patients will be selected that do not have the marker. The question is how reliable would data be on absence of effect. Dr Holland replied that it depended on the frequency of the event but that there are likely to be enough patients to look for adverse events with a frequency of 5-10%.

Predicting liver toxicity: It was noted that, whilst work had been undertaken on predicting and avoiding QT interval changes in patient populations, there had been less industry activity in relation to predicting and screening out problems of liver toxicity. Dr Holland agreed that, although his company had explored predictive markers for liver toxicity, there was not a simple test available at this time.

Safety sample sizes: Asked about concerns that regulators are likely to expect large safety samples for products developed using pharmacogenomic techniques, Dr Holland replied that, whilst the new technology allows efficacy to be proved in smaller studies, a significant volume of patients is still required in order to pick up low volume ADR profiles. An area of particular concern is the 'off label' use of products in patients whose diagnostic test is negative or in the 'grey area'. The example of Herceptin™ had shown that patients in the grey area could sometimes benefit and this raises the question of the number of patients outside the positive group that should be investigated.

A follow-up question asked whether a solution was to undertake safety monitoring after marketing, on a conditional authorisation. Dr Holland agreed that a monitored release could provide an answer but there would need to be a mechanism to distinguish information from correctly selected patients in the population treated.

Microarrays: Dr Robert Pietrusko was asked his opinion on the development of microarray tests that can predict a better response in a subgroup, their usefulness in Phase 3, and whether it will be possible to reduce the number of target genes. Dr Pietrusko felt that it was too soon to predict the value, which will be determined by the sensitivity and accuracy of the test. The development of such tests would be valuable if it appeared that they could predict, for example, that a particular patient has an 80% chance of responding. If there are alternative tests, the benefits will arise from showing that one is more effective than another.

Future markets: A regulatory participant noted the different perspectives that had been presented by the two speakers and asked Dr Holland whether, in pursuing the market for non-personalised medicines, his company felt that predictions were too optimistic when they

foresaw a dominant market for personalised medicines in 5-10 years. Dr Holland expressed the view that stratification of the market would depend a great deal on the type of disease. Oncology is a good example where genomics is helping to develop a profound understanding of the molecular biology of the disease. Previously breast cancer, for example, was diagnosed by origin of the cancer and where it had spread but there are now possibilities to understand the biology of the underlying disease and select an appropriate diagnostic. The 'personalised medicine' approach is being pursued aggressively in cancer and in other areas where there is enough knowledge of the aetiology of the disease, for example in the development of anti-inflammatories.

Dr Holland concluded that there are serious progressive diseases where the mechanism of action of new medicines will be sufficiently well understood to enable them to be marketed in combination with a diagnostic. In other areas he felt that we are still a long way from a degree of understanding that enables relevant connections to be made.

The challenges faced in integrating pharmacogenetic and genomic techniques in drug development

Miss Carly Anderson, *CMR Institute for Regulatory Science*

Carly Anderson presented the results of a CMR International Institute study that had been carried out to collect data and opinions on the integration of pharmacogenomic and pharmacogenetic techniques into the drug development process. Two separate surveys had been addressed to 36 international pharmaceutical companies and to 13 regulatory authorities. Responses had been received from 11 companies and 7 authorities in time for analysis and presentation to the Workshop with further responses expected.

The results showed how and why pharmacogenomic and pharmacogenetics were being applied in the different phases of clinical research in order to:

- Understand the mechanism of action
- Identify new targets;
- Investigate target polymorphisms;
- Stratify patients for susceptibility to ADRs;
- Stratify patients for PK/PD effects.

The rationale for selecting, profiling and stratifying patients for response were also analysed using similar criteria. Information on the tests used for patient selection indicated a significant proportion using company 'home brew' assays (5 out of 8 companies) and CRO home brew assays (7/8). Only one of the 8 companies responding to this question cited the use of approved diagnostic tests and two used academic centre assays.

Five out of the eleven companies had held discussions during drug development with regulatory authorities, predominantly the FDA. Topics discussed included:

- drug metabolising enzyme status;
- improving benefit/risk ratios;
- application and validation of pharmacogenomic technologies;
- improved understanding of clinical results;

The authorities' perception of the benefits of using the new technologies included; increased safety and efficacy, better response rates in defined sub-populations and a better understanding of therapies, leading to improved decision making and disease management. The industry saw benefits in being able to produce more competitive, differentiated products with reduced side effects and size and duration of clinical trials as well as improved benefit risk ratios and enhanced cost effectiveness.

Key issues of concern that were shared by both regulators and industry included the lack of experience and expertise on both sides, the need to provide reliable diagnostic tests

that are validated, sensitive, specific and stable. There were also concerns about the interpretation of data, how to handle findings of uncertain significance and the implications for labelling.

Looking at the future impact of pharmacogenomics, the majority of authorities predicted that increased human and financial resources would be needed, with increased requirements for scientific advice. It was envisaged that there would be improved benefit/risk decision making. From an industry perspective some companies (but not the majority) predicted that financial cost would be reduced over the next ten years and that development times would shorten. There was, however, a majority view that the new technologies would lead to reduced attrition rates in Phases 2 and 3 and improved benefit/risk decisions.

On the question of the help that authorities could give industry the companies gave priority to continued dialogue through forums and workshops, a collaborative approach to the development of guidance and collaboration on an agreed approach to the interpretation and validation of technologies. In the regulators view, additional elements are the procedures for providing Scientific Advice but also the ability to share data and concerns through informal channels.

Asked about the need for regulatory guidance there was very little support for definitive guidelines at this stage although the majority of both companies and authorities would welcome general guidance. The preferred approach identified by both parties, however, was more interaction across authorities and more interaction between industry and authorities.

Points from the discussion

Opening the discussion, the Chairman, Dr Jefferys remarked that this was an important study that bore out concerns expressed recently by the UK Human Genetics Commission on the need for a closer examination of the 'home brew' issue.

The patients' viewpoint: Carly Anderson was asked whether the survey had attempted to address the viewpoint of the patient as a driver in the use of screening tests, and whether there were other sources of information on the views of patients. Miss Anderson replied that this was outside the scope of the CMR study, and Ann Raven, who addressed related issues in her presentation noted that, at present, it is hard to find GPs and patients or patient groups that can act as spokespersons on this issue. Another discussant added that the patients' role would be of increasing importance and suggested that their views should be included in any future Workshops or surveys.

Acceptance by physicians: Asked about the attitude of physicians, Miss Anderson noted that one of the major concerns raised by both authorities and industry was the acceptance by physicians of pharmacogenetic testing that would add another layer of complexity to the work of practitioners. Another discussant on this subject asked whether companies had recently organised forums with practitioners and what feedback had been received.

Replying, Dr Holland said that his company had organised several such meetings, particularly in cases where it was suspected that a product's efficacy would be limited to a subgroup. This was in the face of scepticism from colleagues that physicians would not want to invest the necessary time and effort to educate themselves and apply the necessary tests. In fact, they found little resistance from physicians that deal with patients with life threatening or crippling diseases where therapies under development have the potential to halt the disease process. In other areas there are, however, considerable concerns about making medicines available with a diagnostic in order to avoid serious adverse events, if there is no certainty that the test will be used.

Dr Pietrusko added that physician cooperation could be expected if use of the test was part of a specific risk management programme or where costs could be minimised but it was unrealistic, at this time, to expect a test to be used, for example, to ensure that an antihistamine was more likely to work.

The Chairman added that, from a UK perspective, the matter raises significant policy issues in relation to healthcare delivery systems and changes that may be brought about in the role not only of the physician but also the pharmacist.

The impact of pharmacogenetics and pharmacogenomics on clinical trials

Dr Duncan McHale, Pfizer

Traditionally clinical trials have been designed to demonstrate the ratio of efficacy and adverse reactions in relation to the total patient population. From the individual patient's perspective, however, the outcome is perceived not as a ratio but as a single, personal response: the medicine works, is ineffective or causes an adverse reaction. Using this analogy, Dr McHale discussed the concept and reality of developing 'personalised' medicines through the application of pharmacogenomics and examined the way in which the new technology is likely to change the design of clinical trials.

The promise of pharmacogenetics lies in the fact that physiological systems are tightly controlled by genetic makeup, DNA is stable and does not depend on the tissue type, and genetic variants are easy to measure. There is not, however, enough experience across development programmes to know how predictive it will be in practice. The impact that pharmacogenetics has on clinical trial design will therefore reflect this need to learn more about how to apply the science, and short term impacts may not reflect long term changes.

In Phase 1, pharmacogenomics has the potential to provide a new 'set of tools' to understand pharmacokinetic (PK) variability. Knowledge of the effect of genotype on the maximum tolerated dose (MTD) will allow wider dose ranges to be taken into patients. Broad consent can be obtained for all drug-metabolising enzymes and drug transport proteins. (DME) genotypes are generally regarded as being of low informational risk with a result that samples and data can be handled as other trial measurements. It is important, however, to keep samples until the drug is approved.

In Phase 2, rather than defining an 'average' therapeutic index in a small number of subjects, as at present, the objective will be to identify the effects of genotype on safety and efficacy. This may need an increase in size to allow detection of these effects and even an extension to other centres or countries to ensure that the genetic variation of subjects within the trial reflects the target population. In some respects programmes may be smaller (shorter) through the elimination of likely non-responders, but there is the question of how much safety data will be required for the target population and the non-target population. Other issues arising in Phase 2 relate to the handling, coding and storage of samples and the need for additional informed consent to define the scope and use of those samples.

It is in Phase 3, however, that Dr McHale predicted the pharmacogenomics would make the most significant changes. There is the potential to allow the development of compounds that would previously have been terminated because of rare but severe adverse reactions, because of a narrow therapeutic index, or because efficacy across the whole population is too small. It can also be envisaged that compounds with effects on QT prolongation or potential hepatotoxicity could still be pursued. Such products would, however, require the co-development of diagnostic agents and will involve more complex prescribing algorithms and practices.

Other issues discussed in relation to Phase 3 trials included: the scope of informed consent; the use of genotyping as an inclusion factor; the implications of using a comparator product that also needs a PG diagnostic test; the size and composition of the safety database; and the ability to bridge studies across different countries and ethnic groups.

Dr McHale emphasised the need for a harmonised approach to the many issues that need to be resolved, including:

- The usage of a common terminology;
- Agreement on common elements which should be incorporated into protocols that include collection of genetic samples;

- Agreement on common elements which should be included in informed consent documentation when collecting genetic samples;
- Increased clarity over the scope and use of samples;
- An understanding that it is generally not possible to predetermine all the genes or genetic variants that are likely to be tested.

In order for all of society to benefit from pharmacogenomics it is important to try and reduce any unnecessary hurdles to its implementation. A harmonised approach by all parties concerned would aid in this aim of reducing unnecessary hurdles and also offer the potential benefits resulting from the use of PG to the greatest number of people.

Points from the discussion

Opening the discussion, the Chairman, Dr Jefferys, suggested that one of the messages from the presentation was that industry must expect 'short term pain leading to long term gain' with the possibility that there might be an extension of phase 2 studies in order to reap the ultimate benefits of the new generation of medicines.

QT Prolongation: It was suggested that problems of QT prolongation leading to *torsade de pointes* may be more dependent on the patient and disease than on the characteristics of the drug substance. In response, Dr McHale agreed that there was considerable variation between patients and whereas a small increase in QT interval will lead to an episode of *torsade de pointes* in some individuals, others are unaffected by much larger increases. Pharmacogenetics might hold the key to understanding these inter-patient differences and it might be more important to determine why some patients are susceptible to *torsade de pointes* rather than how likely they are to experience increased QT interval.

Taking the less specific case of hepatotoxicity there is currently little information on how 'generic' hepatotoxic mechanisms are and the extent to which they are related to a particular drug or underlying metabolic factors. There are hints that some groups of patients may be more prone to abnormalities and hepatic events but this is not easy to investigate in the absence of good collections of DNA from subjects with a tightly defined adverse drug reaction phenotype. Data from 500 to 1000 subjects might, however, be needed to draw conclusions and such data are very difficult to obtain for ADRs occurring in only 1 in 100,000 patients.

Interpretation of data: A question was asked about the ability of regulatory authorities, at this early stage of the new technology, to interpret pharmacogenomic data. If, for example, a side effect is signalled at an early stage in a toxicology programme, or in Phase 1, and a pharmacogenomic study is set up that generates some 30 million data points to identify genetic predisposition to this side effect, what should be done with the data. Will the regulatory authorities take the data on trust, will they carry out their own analysis or will they merely take note of it but require to look at basic clinical data.

Replying, Dr McHale suggested that, in this learning period, this is not only a dilemma for the regulatory agencies. The company also faces the ethical issue of how much reliance to place on a test that could be giving misleading information. The ten percent of patients who may be at risk can be removed but it is still necessary to study the risks in the remaining 90% of patients.

In a follow-up question it was noted that the CMR survey had indicated that a number of companies had submitted applications containing pharmacogenomic/genetic data and it would be interesting to know if this data is prospectively submitted and being used proactively.

Dr Eric Abadie, AFFSAPS, France replied that, as far as regulators in the EU were concerned, and leaving aside the well-known cases of Glivec™ and Herceptin™, nobody had had the occasion to give a regulatory opinion based on pharmacogenomic/genetic data. Approaches from several companies had been received to obtain advice and, at this stage,

the CPMP pharmacogenomics working party is seeking *informal* dialogue with companies without any regulatory implications,

**Understanding the genetic and genomic information collected from clinical trials:
Enhancing clinical utility through genomic medicine**

Dr Christopher Chamberlain, Roche Products Ltd

Referring to the department of Genetics and Integrated Medicine within which he works, Dr Christopher Chamberlain commented that 'integrated' appears to be 'the name of the game' at this time. Having heard discussions on the types of information that genetics and genomics can provide within clinical trials, Dr Chamberlain discussed how to 'deconstruct' this information and begin to build a conceptual framework to anticipate how best to use this information for the future.

In this 'peri-genomic' era, with the sequencing of the human genome completed, sequencing capacity has been freed up and refocused on looking at inter-individual variability and differences in genetic sequences. Major resources from academia and industry are being invested in this science with the result that new diagnostics will be delivered that are profoundly influenced by an understanding of genetics and genomic variability. Dr Chamberlain emphasised, however, that these genetic and genomic diagnostics should not be seen as standing alone; they have to be interpreted within an integrated framework as part of a wider understanding of what is going on in the clinical condition and the therapeutic process.

Whilst the utility of the diagnostic information that the new technologies bring is well understood the 'prognostic' element that they bring has novel utility. There is the prospect of being able to make predictions in terms of disease predisposition if the patient is not treated and response predisposition if the patient is treated. It is this latter capacity, the ability to predict response, that is providing the challenge to the way clinical trials are designed and planned. The predictive element, however, needs to be determined in early development in order to know if genetics will have utility for late development studies in Phase 2B and 3.

There are two approaches that can be adopted. Individuals can be divided by genotype and their response measured or divided by response and their genotype studied. The most usual approach is to divide individuals by response as this allows maximal power in terms of phenotypic selection. More importantly because this involves a single call of differentiation in terms of a phenotypic parameter, complex underlying genetic patterns (such as haplotypes) can be constructed to explain that phenotypic variation. This approach also has the advantage that not everybody in a trial needs to be genotyped to deliver the initial hypothesis.

Turning to the clinical utility of the genetic data from clinical trials, Dr Chamberlain identified four elements:

- Seemingly homogeneous diseases can be unpacked to see that there are, in fact, various phenocopies: clinically similar subtypes with different aetiologies requiring differential treatment;
- By predicting disease predisposition it is possible to design clinical trials that determine whether a treatment has a preventative capacity without having to undertake exceptionally large scale trials;
- Predicting drug response predisposition (both beneficial and related to adverse effects) allows stratification of treatment and can support 'drug rescue' where non-responders and those at risk of adverse reactions are screened out;
- Capacity for monitoring disease progress can be enhanced and drug response detected at an earlier stage which allows earlier proof of efficacy and earlier delivery to clinic.

Dr Chamberlain stressed the importance of involving all stakeholders in discussions of this new era of clinical investigations in view of the potentially sensitive nature of the information

about individuals that is being collected. This involves patients, key opinion leaders in clinical practice, regulatory authorities and industry. In order to be successfully introduced into clinical practice, medicines that are based on genetics and genomics and are accompanied by diagnostics must not only be underpinned by valid science but also have demonstrable clinical utility in meeting unmet needs. Such medicines also need to have societal acceptance. Recognising the need for better understanding of, and dialogue about, the new science, Roche Genetics has prepared an education programme on CD which has been given wide distribution.

In conclusion, Dr Chamberlain anticipated that we are moving to an era of targeted therapies that may require more complex differential diagnoses but will mean for both physician and patient better informed therapeutic choice and consequently improved outcomes.

Points from the discussion

Role of lifestyle: Asked about the role of lifestyle factors in pre-disposition profiling, Dr Chamberlain agreed that lifestyle management must be taken into account in developing a holistic response to disease. The questioner suggested that this could challenge the role of the various stakeholders, industry, physician and regulator since delivering holistic solutions would need be some sort of restructuring of responsibilities. Dr Chamberlain felt, however, that this is beyond the scope of those in an organisation that is developing diagnostics and pharmaceuticals, but it, nonetheless, served to illustrate the wider issues that will emerge from 'unpacking' the genetic data in clinical trials.

Prospects for success: A participant commented on the fact that there are relatively few examples of successful products based on pharmacogenomics. In view of the enormous complexity that genetic research adds to the development process, Dr Chamberlain was asked if he felt the new technology might prove more of an impediment than a success factor for industry. Replying, he pointed out that, notwithstanding the complexity of individual responses to any medicine there were many drugs with relatively universal applicability. One of the barriers to making progress in producing viable, targeted medicines is the expectation that prognostic indicators will have absolute utility in indicating who will and who will not respond. A more realistic approach is to expect that genetic diagnostics will provide additional elements of data that can be combined with the traditional diagnostic package in order to enhance its informativeness.

Utilisation of diagnostic tests: the benefits and consequences

Dr David Feigal, Center for Devices and Radiological Health, FDA, USA

Dr Feigal was unable to participate in the Workshop but provided his presentation in the form of a video and accompanying slides.

In his presentation, Dr Feigal described the way in which *in vitro* diagnostics (IVDs) are regulated by the FDA's Center for Devices and Radiological Health and the relationship between the evaluation of drugs and biologics and the control of the genetically based IVDs that are expected to be marketed alongside a new generation of 'personalised' medicines.

The overall mission of FDA includes ensuring the safe use of experimental products, assuring manufacturing claims and approving marketing claims. In the case of diagnostic tests, the assessment of safety must take into account the way in which the test is being utilised and the way this affects the medical care that is being delivered. Standards are set for manufacturing and quality requirements but the most important regulatory drivers are the claims that the company makes about its product in relation to safety quality and effectiveness and other product characteristics.

Dr Feigal reviewed the claims that might be made for a diagnostic, including the ability to determine or predict: the risk of disease, preclinical disease, diagnosis, disease subsets, therapeutic response, disease progression and adverse experiences. Conventional test such as cholesterol monitoring provide a pointer to risk of cardiac disease but the new generation of genetic-based tests should be able to identify genes or the expression of proteins indicating a metabolic process that increases risk. It is possible, particularly looking at gene expression that diseases could be picked up before they appear as clinical manifestations. Increased specificity in being able to diagnose disease and identify subsets can be anticipated. Having such knowledge before initiating therapy is the key to personalising the therapy.

Turning to the way that the claims made for medicines and devices are covered in regulations, Dr Feigal stressed that evaluation in the US is an evidence based endeavour. For diagnostics, the type of evidence is determined not only by the claim but also takes into consideration the risk and the degree of novelty. A claim that has never previously been established will require more evidence although he pointed out that there were special conditions that could apply in the case of products addressing unmet need.

The regulatory system is based on somewhat 'arcane' rules that have resulted in a variety of different types of authorisation. Products that fall into the classification of supporting or sustaining human life or being of substantial importance in preventing impairment of health require full assessment and pre-market approval (PMA). Products that are equivalent to a device or diagnostic that is already on the market and that fall into one of the three classification categories require only a pre-market notification (known as a 510(K) after the relevant section of the Code of Federal Regulations). There are also provisions for humanitarian device exemptions (HDE) for products intended to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States per year.

Dr Feigal compared the requirements for novel drug products or biologics, where the evidence of efficacy must be based on well controlled trials in humans, with the requirements for novel diagnostics. In the latter case the requirements are more flexible. The language in the statutes is 'valid scientific evidence' and reflects the fact that the majority of devices do not require human testing to determine safety and effectiveness or performance standards. There will, however, be many examples of genetic tests that do require human trials and studies in clinical settings. The distinction also needs to be made between *in vitro* diagnostics and those that are actually administered to the patient, such as injectable contrast media or monoclonal antibodies given systemically as a tracer. Systemically administered diagnostics must be authorised by CDER.

Decisions on the safety of a diagnostic reflect a risk and benefit analysis where the primary risk is the consequence of a wrong diagnosis leading to a wrong decision. Issues can, however, go beyond measuring genetic information accurately. The example of cystic fibrosis was cited where information from the test can have implications for reproductive decisions.

Dr Feigal concluded that genetically guided therapy holds great promise, but he believed that the least of the problems is likely to be the development of reliable assays to measure genetic factors or detect proteins that are expressed. The harder part will be to put the results into a clinical context and to find the time and resources for the many research opportunities that the technology opens up. Better, however, to have a wealth of new opportunities than a pipeline that is dry.



Chairman's Summary of Session 1

Dr David Jefferys, *Medical Devices Agency, UK*

The first session had presented several different perspectives on the same theme, and Dr Jefferys observed that there was unanimity in recognising that everyone is on a steep 'learning curve' in determining how to apply the new technology and how to take it forward. There were obviously different views as to whether, and to what extent, pharmacogenomics might shorten or lengthen different phases, and the overall drug development process.

Dr Jefferys expressed the view that there would be critical issues to be resolved in relation to the sensitivity and specificity of some of the diagnostic tests. There are also wider issues concerning this type of testing and the implications for collection and storage of samples. The ethical considerations that are raised and the need for education must not be overlooked.

The discussions had also highlighted issues of applicability and utility of combined diagnostic and medicinal products when used in general practice and primary care. A wider debate among healthcare providers and healthcare educators is obviously needed before industry can address some the practicalities of introducing personalised medicines.

The Session had identified a number of multidisciplinary strategies for those working in preclinical research, those at the cutting edge of molecular biology and those working on clinical programmes. It had highlighted the dilemma of regulators who do not wish to intervene too early, but who are being called upon to give regulatory advice. Also in the picture are those involved in public health issues who must address ways for national health services to move this new approach to medicine forward.

Dr Jefferys also remarked on some new terminology that had been injected into the Workshop during the Session, including the 'peri-genomic era' and 'measured pragmatism'.

SESSION 2. EDUCATION AND REGULATION OF PHARMACOGENETICS AND PHARMACOGENOMICS

Chairman: **Dr Robert Peterson**, *Health Canada*

In his introductory remarks, Dr Robert Peterson referred to the challenges that had been identified in the earlier presentation in regulating and validating the *in vitro* diagnostic tests that would be an integral part of pharmacogenomic-based medicine. These and other regulatory issues would be developed further in the current Session which would address the question of the areas that are amenable to regulation, how much regulation is appropriate and the dynamics of introducing additional controls, as they become necessary.

Pharmacogenetic and pharmacogenomic elements that need to be regulated and validated during drug development: An industry view

Dr Alun McCarthy, *GlaxoSmithKline*

In his presentation, Dr Alun McCarthy used a specific case study to illustrate some of the practical and regulatory issues that had been addressed by his company. Setting the scene, he emphasised the importance of ensuring the right level of regulation at this early stage in the development of the new science. Too much could hinder the development of pharmacogenomics, too little could increase the risk inherent in the technology and this could also hamper development. Dialogue and sharing experience among stakeholders and interested parties is critical to making progress.

The reason for pursuing pharmacogenomic and pharmacogenetic research is to improve the chance of successful research, development and registration, to address unmet medical need and to achieve optimised benefit/risk in identified subgroups of patient populations. Dr McCarthy identified three critical steps: hypothesis identification, hypothesis validation and clinical application. The use of genetic tests is essential for marker testing during hypothesis identification and later in Phase 3, during hypothesis validation. He pointed out, however, that the application of pharmacogenetics during clinical development does not automatically mean that a test will need to be developed for marketing with the product. There are many valid applications of pharmacogenetics, where the science gives insight into the variability in drug response, but does not signal the ultimate need for a test.

The example discussed in the presentation was a satiety agent for use in obesity, which had not exhibited any safety issues in Phase 1. Although not immediately life-threatening, obesity is being increasingly flagged as a major health risk and one where there is an unmet need for safe and effective agents. Furthermore a clear target of greater than 5 Kg weight loss could be set, in response to minimum physician requirements for use.

In Phase 2, however, this progression criterion was not met when a mean weight loss of only 3.7 Kg was seen. Pharmacogenomic analysis, using candidate genes related to the target/mechanism of action, however, identified a 36% responder group with 7.9 Kg weight loss, leaving an approximate 1.5 Kg weight loss in the remainder. No safety issues were found in the selected group and there was no greater incidence of unwanted side effects. This pointed to genetic differences that might not just enhance pharmacology, but might differentiate efficacy from general safety issues.

If the product was to move forward, marketing in association with a test must be envisaged, raising questions of how this is to be made available. There were also questions of recruitment for Phase 3, how robust the Phase 2 data would prove to be, and safety database issues. Having decided to move forward, the provision of DNA samples as an entry criterion is a given, not an option. Furthermore there is no question of anonymising and de-linking DNA data as the pivotal Phase 3 studies require a full audit trail with document verification.

On the question of selective enrolment it was felt that the Phase 2 data was probably not robust enough to justify recruiting only patients with particular pharmacogenetic markers

into the study. There was a very high level of plausibility that one of the markers was the drug target and that variation would affect response, but it had not been proven. It was therefore decided to recruit all comers and stratify the study based on phenotype.

This had implications for the safety database as the indicated patient group made up only one third of the Phase 3 population. Short of increasing the study size by a factor of three (which would have stopped the project in its tracks) the only way for the safety database to be viable was by comparing the safety data in the selected population with the rest of the population.

Another issue to be resolved was the testing that would be required in the post-marketing, clinical situation, and the labelling implications. Testing could be handled by registering an IVD or by requiring tests to be carried out in a suitably accredited laboratory. In view of the difficulties of ensuring that a test was registered to coincide with marketing it was decided that the initial approach should be the accredited testing service, although this did not rule out subsequent marketing of a test. In either case, however, there was the question of storing the collected DNA for development not only of the first clinically available test but also to establish standards for validation of subsequently marketed tests.

This experience highlighted some of the uncertainties that could impact the development of pharmacogenomics. Whereas the company was prepared to propose solutions to the many questions that were raised it was not clear whether these would be acceptable. The project team still felt that specific guidelines were inappropriate at this time but would have welcomed some general guidance or at least a mechanism for obtaining such guidance. This might take the form of informal one-on-one discussions with regulators, but there is also a need to develop some sort of infrastructure that will allow data and experience to be shared in an open and transparent way that would allow all parties to benefit from the cumulative experience.

Points from the discussion

Hypothesis generation: Referring to the case study that had been presented, Dr McCarthy was asked to comment on how the project team 'carved off' the pharmacogenetic markers, until they arrived at the 7.9 weight loss in a given population. Was there a danger of embarking on a 'fishing expedition' to give plausibility to a hypothesis. Replying that 'one man's fishing expedition is another man's hypothesis generation' Dr McCarthy agreed that it is important to be very selective in the candidate gene approach. On the other hand, looking for genetic markers is not so different from seeking other clinical variables, in this example diet, body mass index (BMI) or gender. Genetic markers do, however, often prove to be more useful.

Hypothesis testing: Dr McCarthy was asked about cases where the hypothesis on which a powered Phase 3 study is based proves to be false and the selected sub-population turns out not to be of subsequent interest. He replied that experience has shown that this is most likely to occur with an under powered or possibly biased DNA data set. Lack of experience means that understanding of efficacy markers is not good. Safety issues are likely to have a much stronger genetic component. Fortunately, adverse events are likely to be rare and the old genetic truism applies that the rarer something is the more likely it is to be genetic. There are examples where studies testing safety hypotheses can be replicated but, on the broader question of how reliable these data are, the overall data set is still not large enough to say.

A participant commented that many published papers have shown how unreliable it is to carry out *post hoc* sub group analysis in order to identify patients who respond differently from the whole population. These studies involved several thousands of patients, in contrast to the relatively small studies during pharmaceutical development. Replying, Dr McCarthy highlighted one of the limitations of pharmacogenomics. If one was looking at disease genetics the investigation would automatically include studies of twins and family clustering. This cannot be done in pharmacogenetic studies and therefore, when differentiation is suspected, the genetic background information for assessing the plausibility is limited. When

there are more examples of validated markers to support hypothesis validation he anticipated that there would be an 'exponential increase' in output.

Safety studies. Asked about success in understanding the basis of adverse drug reactions Dr McCarthy cited examples where his company had validated approaches that can associate 50% of the observed adverse events. He suggested that, since relatively simple experiments can give this level of insight when only 0.1% of the genome has been studied, the technology has enormous future potential when the remaining 99.9% has been examined.

Need for Guidelines: In his presentation, Dr McCarthy had indicated that definitive regulatory guidance was not needed at this time, but had suggested that some form of general guidance may have a role. Asked to expand on this, he confirmed his view that there are currently too many variables and uncertainties for guidelines to play a useful role. When faced with a major decision, however, such as whether to base Phase 3 studies on 'all comers' or selective recruitment, it might be useful to have some way of knowing if you are on the right track, in terms, for example, of chronic vs. acute disease, life threatening vs. non life threatening conditions and efficacy vs. safety evaluations.

'All comers' in Phase 3 Studies. Referring to the anti-obesity drug in the case study, Dr McCarthy was asked about the rationale for deciding on an 'all comers' Phase 3 study when there was such a large signal, from the Phase 2 study, for efficacy in the patients with the identified marker. In reply he suggested that this a question of how likely the data are to reproduce. If you identify a subset but the marker sets are wrong then you obviously have a disastrously bad Phase 3 programme. If, on the other hand, you have definitive confidence in the validity of the markers you can probably move forward. For example, if you have identified and validated the existence of poor metabolisers who will be at risk, they can be taken out of the programme which can, with sufficient safeguards, then move to Phase 3.

If, however, you are not one hundred percent sure because it is a new marker which could be an artefact or might not be reproducible in all ethnic groups, it would be a major risk to go forward into a Phase 3 programme on the basis of the assumption. The choice you have is to take an all comers in Phase 3 or do another Phase 2 study and wait three years.

Pharmacogenetic and pharmacogenomic elements that need to be regulated and validated during drug development: A regulatory view

Dr Marisa Papaluca Amati, *European Agency for the Evaluation of Medicinal Products*

Emphasising that she was providing 'a' regulatory viewpoint, not 'the' regulatory viewpoint, Dr Marisa Papaluca Amati outlined some of the activities and discussions with which the EMEA has been involved through the CPMP and its pharmacogenetics working group. The agency is engaged in discussions of a wide range of scientific possibilities that are opened up by the new technologies, from the aetiology of diseases and predictions of disease susceptibility to the development of gene therapy. In line with the theme of the Workshop, however, Dr Papaluca Amati confined her presentation to the application of genetics and genomics in the development of targeted or personalised medicines.

A critical starting point for the CPMP had been the agreement of definitions (*CPMP position paper on terminology in pharmacogenetics, London, 21 November 2002, Reference EMEA/CPMP/3070/01*):

- **Pharmacogenetics** is the study of inter-individual variations in DNA sequence related to drug response;
- **Pharmacogenomics** is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

Although many aspects of pharmacogenomics are new, the need to take account of variability in drug response is already incorporated into existing CPMP guidance documents. These include guidelines on: pharmacokinetic studies in man; bioavailability and bioequivalence; and drug interactions. The concept is also integrated into the ICH guidelines on dose-response information to support drug registration (E1) and ethnic factors in the acceptability of foreign clinical data (E7). Dr Papaluca Amati noted that one of the tasks of the CPMP working party would be to revisit the relevant guidance documents and decide on the need for updates and amendments.

There are also many drugs that are not new, where investigation of variable efficacy and adverse effects has pointed to differences in enzyme expression. These include: haemorrhage and warfarin (CYP 2C9); toxicity/lack of effect and antidepressants (CYP2D6); lack of analgesic effect and codeine (CYP2D6); and prolonged sedation with diazepam (CYP2C19). The integration of pharmacogenetics into pharmaceutical R&D should therefore be regarded as 'evolution not revolution'. A brief survey of 116 randomly selected new drug submissions had been carried out and it was found that pharmacogenetic investigations were reported in 27. Of these, there were nineteen cases where there were consequences for the labelling (Summary of Product Characteristics), predominantly related to information on drug interactions.

Reviewing the recent history of developments involving the EMEA and CPMP, Dr Papaluca Amati referred to a seminar convened in 2000 which had brought together the Commission, patient groups, industry and academia. The CPMP work on definitions and terminology had been a direct result of that Workshop. With respect to international activities, the EMEA has been represented on the CIOMS Working Group on Pharmacogenetics since 2001 and participated in a FDA workshop in 2002. A joint Workshop with EFPIA, organised by DIA, is planned for October 2003.

An important current undertaking is the conversion of the CPMP paper on terminology in pharmacogenetics, which also deals with the handling of DNA samples from clinical trials, into lay language with the objective of providing a document for patients and ethics committees. This is being assessed for readability and will be reviewed by the *Plain English Campaign* before being translated into the eleven languages of the EU.

The EMEA/CPMP has established an *ad hoc* pharmacogenetics working group that is chaired by Dr Eric Abadie and includes geneticists, pharmacologists, toxicologists, ethicists and experts in clinical methodology. A concept paper has recently been issued³ setting out the procedure for briefing meetings between the expert group and companies. These will provide an informal forum for highly confidential discussions between sponsors and regulators on jurisdictional, regulatory and scientific issues related to development projects.

Dr Papaluca Amati outlined some of the 'dos' and 'don'ts' that regulators should observe at this early stage in the development of the new technologies. Firstly, it is not the business of regulators to pre-empt evolution in the science or the way it is reshaping business. They should not be putting obstacles in the way of progress and new regulatory requirements should not be drawn up in the absence of appropriate experience. On the other hand, regulators cannot afford to take either a 'wait and see' stance or an over reactive one. Her recommendations for the regulators 'do' list were:

- gain experience as the technology evolves;
- explore the impact on medicines development;
- identify and secure adequate expertise for regulatory evaluations;
- identify, in dialogue with stakeholders, priorities for guidance on data and the level of evidence required.

³ EMEA/CPMP/4445/03 Concept Paper on Pharmacogenetics 'Briefing Meetings', 24 March 2003

Points from the discussion

CPMP activities: Dr Eric Abadie added a comment to emphasise the nature of the proposed briefing meetings with industry. These are not analogous to FDA IND discussions which involve the submission of data and are a formal procedure. The briefing meetings will be strictly informal with no minutes and follow up in the CPMP. He also endorsed the comments made that it was premature to consider formal guidelines in the absence of specific experience.

Industry sectors: Referring to the submissions that include pharmacogenetic data, Dr Papaluca Amati was asked whether there was a significant difference in the numbers of submissions and discussions relating to proteins (biotech industry) compared with traditional small molecules. She replied that the large majority of examples under discussion were small molecules which might be expected as the focus is on metabolising enzyme polymorphism pathways which might be less relevant for proteins.

Regulation of Tests: Dr David Jefferys commented on the current situation with regard to the regulation of *in vitro* diagnostics (IVDs) in the EU. The European IVD Directive, which comes into force on 7 December 2003, will require not only that tests are validated for sensitivity and specificity but also that the laboratories and services undertaking the tests meet the required standards. The requirements for registration and CE marking for laboratories and services applies equally to commercial enterprises and to those operating within the health services.

There are issues, both within the EU and at international level, with variability in the sensitivity and specificity of tests and this will be addressed by the Global Harmonization Task Force (GHTF) - the medical devices equivalent of ICH. As regulation moves forward in Europe, genetic tests may need to be classified under Annex 2 to the Directive which means that common technical standards will be required and the question of harmonisation will become more pressing. Dr Jefferys emphasised the importance of dialogue between those involved in pharmaceutical regulation and diagnostic regulation. The two sectors need to move forward together or there will be serious gaps in the regulatory controls.

Dr Papaluca Amati added that a day's session at the DIA Eurometing, March 2003, had been devoted to statistical modelling and new methodologies for validation of pharmaceutical/diagnostic combinations. There are two separate issues; the need to ensure that tests are relevant, in terms of the genetic polymorphism that is tagged during drug development, and the need to ensure that a valid, reproducible and consistent test can be produced for clinical use after marketing.

CPMP Terminology discussions: A participant commented that it was an unusual step for the regulators to undertake discussions on terminology with ethics committees and lay parties in the way the CPMP was proposing. Dr Papaluca Amati replied that this was a sign of the changing regulatory environment in which it is increasingly important to have feedback and dialogue with other stakeholders.

Briefing meetings: Asked whether many sponsors had taken up the proposal for informal briefing meetings with the CPMP working group, Dr Papaluca Amati replied that there were three in the queue. Since only three meeting sessions a year are currently planned a waiting list must be established on a 'first come first served' basis.



**Pharmacogenetics evaluation project:
The information gap between the regulators, prescribers and patients
Ms Ann Raven, *University of Cambridge, UK***

The two year project described by Ann Raven was funded by the Wellcome Trust Bioethics Programme, and brought together a team with expertise in health policy, public health, health technology assessment, management science, information technology and in the health and policy implications of the new genetics. International in scope, the assignment included a programme of literature reviews, interviews (in the US and Europe) and focus groups of all pertinent constituencies.

The objectives were:

- To investigate the requirements for the delivery of accurate, transparent and timely information about pharmacogenetics and its products at three levels of health service activity: doctor and patient; health service 'commissioners' for priority setting; and statutory regulators;
- To consider the policy implications of the information requirements that will arise. The pharmacogenetic products within the scope of the project included diagnostic tests, drug products, and test-drug combinations. The project was directed towards policy makers in health administration, regulation and industry who will be involved in the decision making process as the new technologies develop. The stakeholders who were consulted included representatives of government, regulatory authorities, industry, research (clinical pharmacology and pharmacogenomics), prescribers, ethicists, economists, patient advocacy groups, bio informatics experts, geneticists, public health and health technology assessment (HTA) bodies.

Two strikingly different perceptions of pharmacogenetics were encountered. There were those who saw this as a unique and clearly distinctive new branch of science that could transform the practice of medicine, but which also brought new and complex regulatory and ethical issues that need to be resolved. To others it was perceived as an important development, but in reality only another prescribing tool to be integrated into clinical pharmacology, health professionals' education, postmarketing surveillance and other elements of the existing infrastructure.

At the same time, clinical pharmacologists and others involved in research cautioned that the science is still at an uncertain stage and that it would be premature to rush into decisions affecting the way it should be developed. Although a primary focus of the new developments would be to prevent serious adverse events associated with medication, there was considerable concern that the risk to patients would actually increase as a result of being prescribed medicines 'off label' without the appropriate tests being applied.

Many patient representatives felt that the new generation of medicines would be more readily accepted if it could lose the 'genetic' label which can give rise to unnecessary worry and misunderstanding about the nature and purpose of the tests. Whilst recognising the benefits of medicines tailored to their own genotype, patients were concerned about use and storage of test results that might hold sensitive disease-related information.

From the physician's perspective a new generation of medicines with better defined and more specific mode of action would be welcome provided the clinical validity and utility is adequately demonstrated. There was, however, a wish to understand the implications of not carrying out the tests, both in terms of patient safety and the physicians' liability. Currently, there is a lack of information about the cost implications of the new developments and Ms Raven noted that, when medicines requiring pharmacogenetic tests start to appear on the market, physicians may find the guidance given by HTA bodies more pertinent than the regulatory information provided in the product labelling.

The project had identified factors that could form barriers to progress in this field of development. These included a lack of investment in functional science and commercial 'tensions' among industry and healthcare providers about the economic implications of a new

generation of medicines that might have significant health benefits, but at the cost of smaller markets for the companies and increased infrastructure requirements for health services. It was also noted that confidentiality and data privacy rules, whilst important, are making it increasingly difficult to collect vital evidence for the health research studies needed to further the new science. The inadequacy of computerised patient record systems is also a considerable impediment.

From a regulatory point of view the need to review the control exercised over the new genetic diagnostic tests was highlighted. In particular, there is concern about validation of the so-called 'home brew' assays and oversight of the establishments that offer testing facilities. The development of special regulatory procedures, if needed at all, for the products themselves may only move forward once there is data on more products in late development.

Finally, there is an urgent need for education programmes on the emerging technologies for patients, and healthcare professionals, including pharmacists and nurses and those involved in ethics committees. Some initiatives have started in this area but, as with regulation, the educational drive requires the impetus of products reaching the market when the 'vision' of the new technology will become a reality.

Points from the discussion

Decisions on cost effectiveness: it was suggested that the move towards giving more decision-making power to the patient seems to be incompatible with cost effectiveness being decided by a third party. It would appear difficult for personalised medicine to live within a state-delivered healthcare system that takes decision making away from the patient. Ms Raven acknowledged that there is a real tension between healthcare systems that use a public health paradigm and the demands of individualised medicines. Patient demand is going to be a major concern for primary care workers and this will become more of an issue if patients are able, via the Internet, to obtain genetic test results whether valid or invalid.

Genetic discrimination: The question was raised of whether selection of patients on the basis of their genotype could give rise to accusations of racial and other discrimination on the basis that the medicine had not been tested for a particular race or genotype. Ms Raven agreed that a potential problem existed with genotypically defined minorities which may not necessarily be racial. Patient groups and ethicists are concerned about this but it is, perhaps, more of an issue with ethicists. The problem, in fact, already exists in that medicines are tested in one population and may not have been subject to bridging studies in other populations. Furthermore patients may already be excluded from treatment with certain medicines on grounds of age and pre-existing conditions, but discrimination because of genotype is likely to be a more sensitive issue.

Empowering patients: A participant commented that educating patients about the safety benefits to be derived from personalised medicines might also lead to companies and physicians being sued if the prescriber ignores the instructions and the patient is exposed to unnecessary risk. Ms Raven replied that the empowered patients will find information and educate themselves. Concerns about more litigious patients may, however, be justified, especially if the trend seen in the US spreads to Europe.

Acceptable risk: The converse situation was suggested, where a patient who tests negative for a therapy, but is aware that the science is not an exact one, may be willing to accept, say, a 10% chance that the product will be effective. In this situation, Ms Raven suggested, a deciding factor might be whether the treatment will be financed or reimbursed under the patient's healthcare cover or national health service.

Predisposition to disease: Ms Raven was asked to comment on the ethical aspects of using tests that not only identify pharmacogenetic markers but also give information on disease susceptibility. She replied that there appear to be more concerns in the US than in Europe about the misuse of such information by employers and insurance providers. It does, however, raise the question of whether patients need to know, at the time of giving informed

consent, the implications of tests that give information beyond the immediate scope of the trial.

Healthcare implications: A participant commented that neither public nor private healthcare systems would be able to provide the testing resources needed for personalised medicines. There might be a case for only including a specific requirement for a screening test in the authorisations for products where there are compelling safety and efficacy issues. In other cases regulators might decide that testing is not essential.

Regulatory implications of stratifying patients enrolled into clinical trials based on pharmacogenetic and genomic profiles

Dr Robert Temple, Food and Drug Administration, USA

Dr Temple was unfortunately not able to travel to the Workshop because of the prevailing international situation but kindly provided a detailed presentation in the form of the slides

Dr Robert Temple had been asked to address questions about the acceptability of stratification, the regulatory implications, whether selection and stratification should be based on efficacy or safety alone, and how many patients will be needed. The latter question was deemed unanswerable, but the others were covered in a comprehensive overview.

Selection of patients based on likelihood of response is generally called enrichment. Enrichment can be practical (patients likely to come to clinic) or pathophysiological (heart failure patients with systolic rather than diastolic dysfunction). Enrichment can raise questions of generalisability, however, and it may be useful to study not only people with a characteristic making them likely to respond, but others as well. In this case, it is useful to stratify by the characteristic. Stratification of patients based on pharmacogenomics is not only acceptable but it is not really so new. Genetic selection is simply a novel enrichment characteristic. A critical distinction with respect to the use of genetic information is whether the information is used prospectively, as a stratification variable (the easy case) or retrospectively, i.e., after the study is over (more difficult).

On the question of selection based on efficacy or safety, most discussion to date has focussed on genetically identifying likely responders and on showing effectiveness in that group, but the identification of people who are genetically at risk could also be of great value and either selection process could be used. In both cases a critical question in trial design is how much evidence you need about effects in the 'off' group, that does not respond or that gets an adverse effect.

Looking at prospective stratification, two scenarios were examined, first where the genetic characteristics are known prior to randomisation and secondly where the baseline characteristic is not identified until after randomisation but still before the study is complete (a 'minor' variant that would occur, e.g, when the test took a long time to complete). As noted, enrichment of studies is common. Examples of 'practical' enrichment include: finding (prospectively) likely compliers and choosing people who will not drop out; eliminating patients with diseases likely to lead to early death; eliminating those already on drugs with similar effects to the test drug, etc. Examples of commonly accepted 'pathophysiological' enrichment based on understanding of the disease were also provided. These include choosing oedema of only cardiac origin when studying an inotrope, distinguishing congestive heart failure resulting from systolic or diastolic dysfunction and separating high from low renin states in hypertension. A well-established genetically determined difference could be a very similar basis for a pathophysiologically selected (enriched) population in a clinical trial. The most convincing examples to date involve tumour genetics (e.g., HER2+ breast tumours), but there could be somatic examples too. Pathophysiologic enrichment can be applied after randomisation but still be considered 'prospective'. The example was given of testing antibiotics in a pneumonia population when, initially, it will not be clear whether the infection

is bacterial or viral. Typically the evaluation of efficacy will be based on the subset with documented bacterial infections.

A critical distinction when using prospectively enriched populations is between cases where only people with the characteristic will be treated and cases where everyone must be treated although only some can respond. In that case, safety issues are pertinent to the whole population and it must be at least considered that one should examine effectiveness in all patients.

In such cases, the subset with the characteristic can be said to provide 'proof of principle' but the benefit/risk assessment must involve the whole treated population. In some cases (sepsis) it appeared that treatments might actually have been disadvantageous to the people who did not have the pertinent baseline organism.

In cases where selection can be made prior to treatment, a study in selected patients can provide both proof of principle and an overall benefit/risk assessment. Generally, some information about the unselected group is useful and, if the selection characteristic is graded (like HER2(-) in breast cancer), there would be interest in the relation of response to marker level. In some cases data would be required in the non-selected patients if it were obvious that the drug could not work in them.

Stratification based on retrospectively identified subsets (demographic, pathophysiologic, or genetic) will rarely lead to a definitive conclusion about the study. On the other hand, such an observation could become the basis for prospective selection in a subsequent trial (confirmation of the *post-facto* analysis).

In cases where there is a persuasive genetic/pathophysiologic marker, measurable at baseline Dr Temple suggested pointers for an overall strategy:

- Stratify patients in studies by marker (+) or (-), '*pre-hoc*';
- Make the effect in the (+) group the primary endpoint;
- Except where pharmacodynamic data make lack of effect in the (-) group completely obvious, evaluate the effect in this group as a secondary observation, looking for a difference in effect size;
- If the 'clear' pathophysiologic explanation only arises *post facto*, a confirmatory trial will almost always be needed but a prospective plan to evaluate a very positive finding in two halves might be persuasive.

Dr Temple's paper focussed on pharmacogenetic predictors of effectiveness but he points out that generally similar considerations would apply to a safety marker. Sample sizes depend on the randomised groups that are identified for testing the primary hypotheses. What is not so clear is how much data are needed in the non-pharmacogenetically selected group. It is necessary to show that there is no effect or a lesser effect in the group and the number needed could depend on response size in the selected patients.



SESSION 3. SYNDICATE DISCUSSION

Chairman: **Dr Mike Clayman**, *Lilly Research*

Note: The Syndicate discussions and conclusions are reported in Section 2: Outcomes. The Session, however, also included the following presentation and discussion.

Pharmacoeconomic implications of personalised medicines

Mr Adrian Towse, *Office of Health Economics*

Mr Adrian Towse addressed the economics of developing and marketing medicines where the target population may be significantly smaller than for the traditional 'blockbuster' product. Citing the current estimate of \$800 million for the R&D cost of each new medicine marketed, he noted that 70% of medicines do not cover these costs. With return on investment being brought about by the top 10% of best selling medicines, there is the question of what happens if, as a result of personalised medicine, that 10% disappears. Some have speculated that pharmacogenomics would result in R&D costs being reduced through better knowledge of disease mechanisms, better candidate drugs, fewer failures with smaller and more targeted trials and earlier licensing. Those actually involved in the R&D process, however, are not currently predicting this saving of time and resources.

Using an extreme example, Mr Towse referred to gene therapy which, if successful would mean a once-only treatment per patient. How should such a treatment be priced and paid for? The health gain for the patient in terms of prolonged life and the quality of that life has a high value, but it is harder to obtain that value from the payer at one time than it is to recoup the value of a medicine that needs to be taken for a lifetime. There is a resistance to absolute price levels for new drugs and a reluctance to link price to the potential value, but there are reasons for this, especially in a competitive health insurance market where the payer that carries the initial cost of treatment may subsequently lose the patient to a cheaper scheme. In monopoly situations, such as the UK National Health System, there are also the constraints of annual budgets. There are contractual solutions where a genetic 'cure' could be paid for over the lifetime of the patient but, in the market place, this might be hard to achieve. The economic incentives for research in this area are therefore extremely low.

The economics of medicines requiring genetic testing are not quite so bleak. Essentially, the payers will be interested in this type of medicine if the savings and health benefits exceed the costs. From the companies point of view, a medicine for a lower target population is only a viable proposition if the R&D costs are significantly lower, which currently seems unlikely, or if a higher price can be agreed reflecting the greater specificity of the product. The economic calculations must take account of such factors as the payers willingness to pay for health gain, the value of avoiding adverse events and the additional cost of diagnostic testing. Even where measurable 'social gain' can be demonstrated from targeting, however, there remains the resistance of payers to high absolute prices.

Mr Towse cited two examples to illustrate the economics of combining diagnostics with medicines. The first was Centoxin™ an expensive treatment for gram negative bacteremia sepsis that was only effective in one third of patients. Furthermore, the product increased mortality in gram negative bacteremia sepsis, and, in the absence of a 'bedside test' for susceptibility, the product was withdrawn. Using a set of equations, Mr Towse illustrated that even if a diagnostic test cost \$11,000 Centoxin™ would still have been cost effective at its price of \$4000 per patient and that a relatively inexpensive diagnostic would, theoretically, made the product cost effective even at a much higher price.

The second example was Herceptin™ which only benefits 25% of patients. The genetic test is inexpensive (less than \$100) and the drug is relatively expensive and therefore it is logical for the payer to chose to test all patients. Mr Towse, however, illustrated that the economic value of testing all patients, would still apply at much lower levels of non-

responders than are found with Herceptin™ (e.g., 1.5%), provided the cost of the test is low in relation to the cost of the drug.

He concluded that, with appropriate pricing and appropriate targeting of health effects personalised medicine is quite compatible with the concept of a 'blockbusters' but this is crucially dependent on whether payers are willing to recognise the concentrated health gain and adjust prices accordingly. This does, however, leave a problem when a group of patients is identified for whom existing therapies or new therapies will not work and patient numbers are too small, even at very high prices, to justify investing \$800 million to develop a tailor made treatment.

Points from the discussion

Cost and value: A participant commented that payers are not moving towards consideration of cost effectiveness but are focusing on cost utilisation. Regardless of the economic rationale that is provided there is simply a limit to the budgets that are available to support expensive therapies whether or not there are 'compelling' data that support their use. Mr Towse agreed that this is a growing concern. Healthcare budgets are constrained and, in Europe and Japan, economic growth overall has been relatively low by historic standards, which adds to the pressure. Budgetary constraints have not, however, been translated into a willingness to focus more on the relationship between costs and value. He suggested that companies, when drawn into arguments over price, have probably not been as successful or aggressive as they could be in demonstrating the value of their products. There is a tendency to dismiss, as inappropriate, payers' demands for information on value for money. If companies are not able to demonstrate value and to persuade those paying for medicines that the prices are fair, they will not get the returns to justify further investment in the sort of products that society wants to see. It is a big issue.

Paying for lifetime health gains: A participant suggested that, where a product has the potential to bring lifetime benefits but the costs are high, industry should encourage patients to turn to a third party insurance company. Mr Towse cautioned that it should not be assumed that a third party insurer is necessarily going to behave any differently from a Government acting as the third party payer. Third party insurers are not insuring people for life. They are taking one year at a time and it would be naive to believe that just switching from public to private necessarily solves the problem of linking payment over a long term.

A final caution: Mr Towse added a final comment on the potential consequences of not investigating pharmacogenetic differentiation during the development process. He proposed a scenario where a blockbuster is on the market for use in all patients when a diagnostic manufacturer produces a test that identifies the 30 or 40 % of patients for whom the drug is specifically effective, potentially eliminating up to 60% of the market. The drug is obviously valuable since its efficacy could be demonstrated in trials where the benefits were concentrated in a limited proportion of the patient population. The price, however, has been negotiated on the basis of a broad market that is now drastically reduced. You therefore have a drug that will give a great deal of value to society but is not going to give the company the returns that were originally expected, whereas extra investigations during development would have revealed a highly targeted effective drug that could have been presented to the payers with a different pricing proposition.

Chairman's comments

Dr Mike Clayman, *Lilly Research*

Closing the Syndicate Session, the Chairman thanked all the Workshop participants for their contribution to the discussions, but particularly the *Rapporteurs* who had had the task of summarising these (*see Section 2 of this report*). This Workshop had taken place at a time when 'we are taking the first steps in what will be a very long journey' and the Syndicate

discussions had brought out many of the crucial dilemmas that both industry and regulators are facing. One of the most fundamental is that, at this stage, researchers are able to generate reams of data without being completely clear how these data should best be applied to enhance patient care and facilitate drug development. Many other dilemmas had been identified, in relation to ethical and socio-economic issues, the regulation and validation of diagnostic tests, and regulatory responses to the evolving data sets. These cannot be resolved in a single CMR Institute Workshop, nor was this the intention, but the Syndicates had met the expectations of the organisers by proposing ideas and suggestions that could be carried forward. These included:

- The creation of a common database for learning;
- The creation of forums for discussion on an on-going basis;
- De-mystifying the topic and adopting a less emotionally charged terminology in order to facilitate education;
- Conditional approvals based on patient sub-sets;
- New standards of requirements for patient information;
- Not introducing new guidelines or 'points to consider' at this stage.

Dr Clayman endorsed the call for a second CMR Workshop to be convened in 2004 and suggested that the focus should be on case studies from industry and status reports from regulatory authorities. Feedback from the CPMP briefing meetings with companies would be of particular interest. Referring to the paper provided by Dr Sato, MHLW, he noted the sentiments expressed, in line with other regulators present at the meeting, that 'fact finding activities in sharing experiences could be crucial to an internationally co-ordinated approach to pharmacoeconomics and pharmacogenetic matters'.

He also noted that it would also be important to create a forum for developing a common nomenclature for pharmacogenomics and pharmacogenetics. For regulatory purposes, this may be something that should be coordinated through ICH but there is also the need, as the Syndicates recommended, for a common language that is clear and simple and can be used to address the issues in lay terms.

