

R&D Briefing

Regulating personalised medicine



39

Highlights of the Workshop on Regulating personalised medicine

**Organised by the CMR International Institute for
Regulatory Science, Nutfield Priory, Surrey, UK,
14-15 April 2003**

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**CMR International
Institute for Regulatory Science**

The CMR International Institute for Regulatory Science has been established 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 the pharmaceutical industry and the 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 (see back cover).

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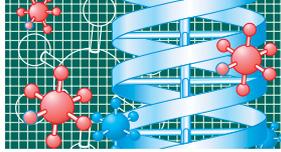
For information on forthcoming Workshops and current and future Projects and Publications visit the website:
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The programme of activities is published in the Institute Agenda, available from the website.

CMR International Institute for Regulatory Science

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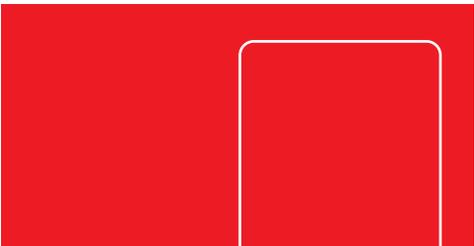
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Regulating personalised medicine

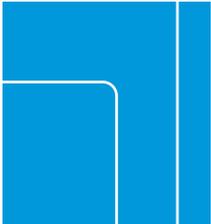
Highlights from the Workshop held by the CMR International Institute for Regulatory Science, Surrey, UK, 14-15 April 2003

Key points



The pharmacogenomic era has begun in earnest and it is no longer a question of whether it will deliver a new generation of medicines, but when.

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 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.

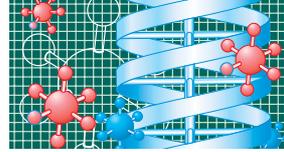
There are also practical and economic issues for healthcare delivery infrastructures in moving towards an era where diagnostic genetic testing, as a prerequisite to prescribing medicines, could become the norm, rather than the exception.



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.

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



Background



The unravelling of the human genome and advances in genetic research are now opening up new horizons in medicines research, at the forefront of which is research on the integration of pharmacogenomics (PGx) and pharmacogenetics (PGt) 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.

These developments have implications for pharmaceutical research and regulation that have not yet been fully explored. 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 Priory, Surrey, UK.

Workshop Recommendations

Four Syndicate Discussion Groups were convened in Session III of the Workshop. Recommendations and discussion points from the Syndicates are reported here.

Database of pharmacogenomics 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 academic attention to pharmacogenetic testing issues;
- Form the basis for state-of-the-art papers on the use of this technology.

Harmonisation of procedures for sample collection, storage and future analysis

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

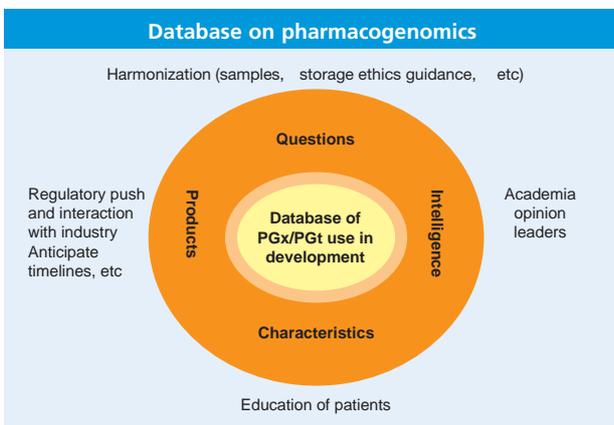
Confidentiality of collected samples and anonymisation and decoding including:

- 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.

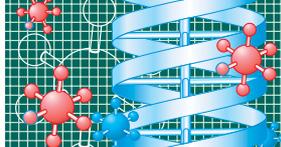
Sample storage and the ability to carry out future analyses on stored samples:

- 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.



From the presentation by Duncan McHale

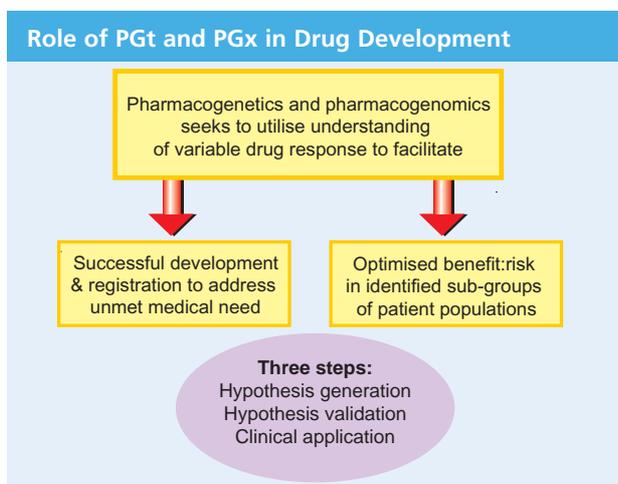


Workshop recommendations



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.



From the presentation by Alun McCarthy

Counterbalancing 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.

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

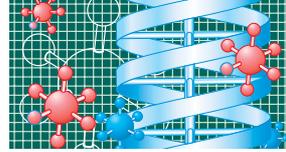
Whilst explaining the nature of these tests openly, they should not be portrayed as significantly different from other diagnostic tests on blood and urine samples that are routinely used as guides in diagnosis and the prescription of medicines.

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.

What do patients want to know?

- Clarity about distinctiveness of PGx
- Potential benefits and disadvantages:
 - Drug selection
 - Appropriate dosing
 - Avoiding toxicity
- How definitive is the result?
- Will test results include disease information too?
- Does the test result impact on my family?
- Who will have access to these data?

From the presentation by Ann Raven



Workshop recommendations



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 III 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 earlier about the need for more appropriate language and terminology is also applicable to patient leaflets and information.

Syndicate Sessions

Chairman: **Dr Mike Clayman**, Vice President, Global Regulatory Affairs, Eli Lilly and Company, USA

In Session 3 of the Workshop, 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**, Director of Strategy Development and Communications, Imperial College, London, UK

Rapporteur: **Simon Larkin**, Director Regulatory Affairs and Safety, Kyowa Hakko UK Ltd

Syndicate 2:

Chair: **Gunnar Alván**, Director General, Medical Products Agency, Sweden

Rapporteur: **Samuel Vožeh**, Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic, Switzerland

■ **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:

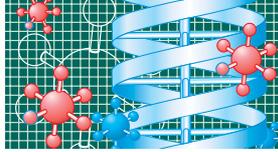
Chair: **Stuart Walker**, Chief Executive, CMR International Ltd

Rapporteur: **Stewart Geary**, Director, Medical Regulatory Affairs and Pharmacovigilance, Eisai Co. Ltd, Japan

Syndicate 4:

Chair: **Michael Zühlsdorf**, Head of Biochemical Pharmacology and Pharmacogenetics, Bayer AG, Germany

Rapporteur: **George Butler**, Vice President and Head, Worldwide Regulatory Affairs, AstraZeneca Pharmaceuticals



Points from the syndicate discussions



■ **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 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.

■ **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 safe-

guards 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.

■ **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.

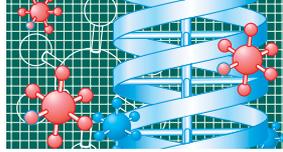
■ **Case-by-case approach:** Recommendations and decisions made on a case-by-case basis are the only feasible approach for a science in its infancy but the question arises of how long this can be sustained. Current discussions of the issues are closely related to individual cases and an assessment of:

- 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.

■ **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



Points from the syndicate discussions



■ **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.

■ **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 when more pharmacogenetic-based treatments become available, there is currently a perceived lack of opinion leaders and academic forums that can offer independent scientific advice.

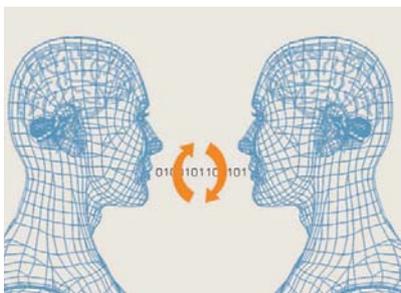
■ **Interaction between pharmaceutical and diagnostic producers:** A significant 'gap' was identified in communication between regulatory authorities and between companies involved with pharmaceuticals and with in vitro diagnostics (IVDs). Firstly there are harmonisation initiatives on guidance and regulation of medical devices and IVDs, through the Global Harmonization Task Force (GHTF) but the discussions do not include 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.

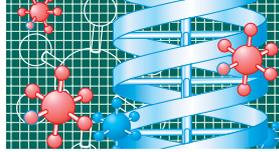
■ **Test validation:** There needs to be discussion on the amount and type of work required to validate pharmacogenetic tests, with a distinction made between those tests carried out for the development of new products and those that are carried through to the market place for routine use with an approved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

■ **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.

■ **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 issue which was recognised as being important and could be the subject of a separate Workshop.

■ **EU Briefing meetings:** Participants had welcomed information on the informal briefing meetings to be held between the CPMP Working party and industry 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.





Points from the syndicate discussions



■ **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 order to provide assurances on safety, beyond the smaller indication.

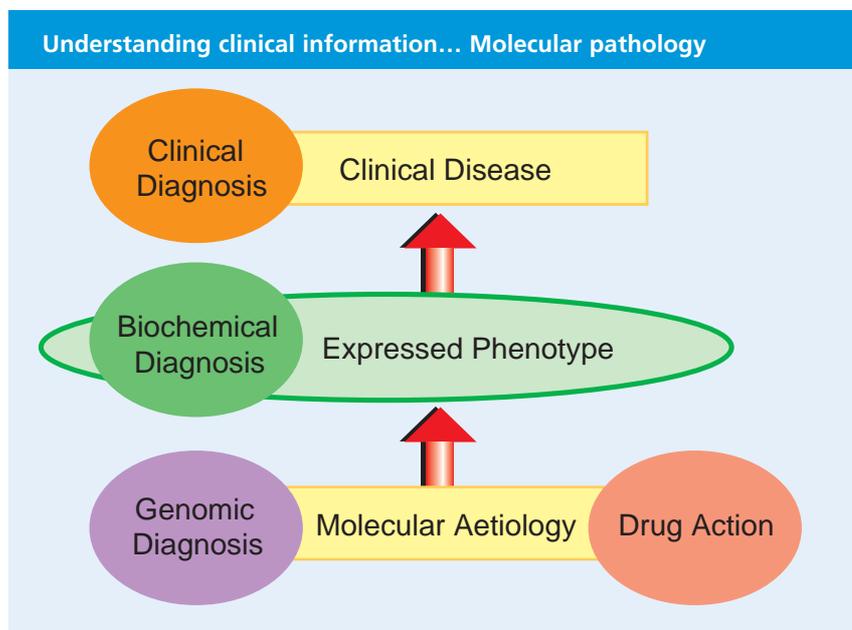
■ **Economics of drug development:** A comparison was made between the investment costs and returns for the current blockbuster drugs and medicines for smaller, targeted populations. It was apparent that the development of medicines for smaller markets is only economically viable if the new technologies 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, 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.

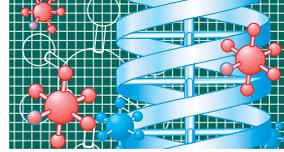
■ **Change in environment:** A 'must' for bringing about a revolution in the way medicines are developed and administered is a change in the general environment for medical treatment. This includes a change in the public perception of risks of medicines, a better understanding of their value and, in 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.



From the presentation by Dr. Christopher Chamberlain



Workshop Programme



PROGRAMME

Chairman: Dr David Jefferys, Chief Executive and Director, Medical Devices Agency, UK

Integrating pharmacogenetics & pharmacogenomics into drug development:

Dr Bob Holland, Vice President, Global Experimental Medicine, AstraZeneca, UK

and

Dr Robert Pietrusko, Vice President World wide Regulatory Affairs, Millennium Pharmaceuticals

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

Miss Carly Anderson, Project Leader, CMR International Institute for Regulatory Science, UK

The impact of pharmacogenetics and pharmacogenomics on clinical trials

Dr Duncan McHale, Director, Clinical Pharmacogenomics, Pfizer Global R&D, UK

Understanding the genetic and genomic information collected from clinical trials

Dr Christopher Chamberlain, Medical Genetics Expert, Genetics & Integrated Medicine, Roche Genetics, F. Hoffmann-La Roche, UK

Utilisation of diagnostic tests: the benefits and consequences

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

Session I: Pharmacogenetics and Pharmacogenomics during clinical development

Quotes and extracts from the Workshop report

In Phase II, 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.

(Duncan McHale)

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.

(Robert Pietrusko)

The discussions had 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.

(David Jefferys)

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.

(David Feigal)

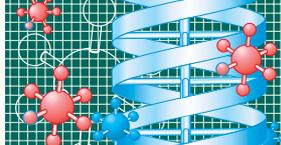
Whilst the utility of the diagnostic information that the new technologies bring is well understood the 'prognostic' element that they bring has novel utility. There is the prospect of being able to make predictions in terms of disease predisposition if the patient is not treated and response predisposition if the patient is treated.

(Christopher Chamberlain)

After some unrealistically optimistic predictions that genomics and genetics would solve all problems, a degree of 'measured pragmatism' is entering into the discussions.

(Bob Holland)

The CMR Institute survey presented by Carly Anderson is reported separately in R&D Briefing No 40



Workshop Programme



PROGRAMME

*Chairman: Dr Robert Peterson,
Director General, Therapeutic
Products Directorate, Health Canada*

*Integrating pharmacogenetics and
pharmacogenomics into drug
development:*

*Identification of the elements and
suggestions as to how these may be
regulated and validated*

*Dr Alun McCarthy, Worldwide
Director, Clinical Pharmacogenetics,
GlaxoSmithKline, UK*

and

*Dr Marisa Papaluca Amati, Deputy
Head, Biotechnology and Biological,
EMEA,*

MHLW Perspective

Mr Daisaku Sato, Deputy Director,
Evaluation and Licensing Ministry of
Health, Labor and Welfare, Japan*

Pharmacogenetics evaluation project:

*The information gap between the
regulators, prescribers and patients*
*Ms Ann Raven, Senior Research
Associate, University of Cambridge,
UK*

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

Dr Robert Temple, Director, Office of
Medical Policy, Center for Drug
Evaluation and Research, FDA, USA*

** These participants were unable to travel to the
Workshop but provided their papers and slides.*

SESSION III

*Pharmacoeconomic implications of
personalised medicines*

*Mr Adrian Towse, Director, Office of
Health Economics, UK*

Session II: Education and regulation of Pharmacogenetics and Pharmacogenomics

Quotes and extracts from the Workshop report

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.

(Ann Raven)

In Japan, in terms of developing personalised medicines, the greatest progress appears to be taking place in the field of cancer treatment, both in terms of therapy and avoiding adverse reactions. Due to its life threatening nature and recognised genetic mechanisms, genetic testing is likely to be less of an obstacle to these patients.

(Diasaku Sato)

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.

(Robert Temple)

The European in vitro diagnostics (IVD) Directive, which came 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.

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.

(Marisa Papaluca Amati)

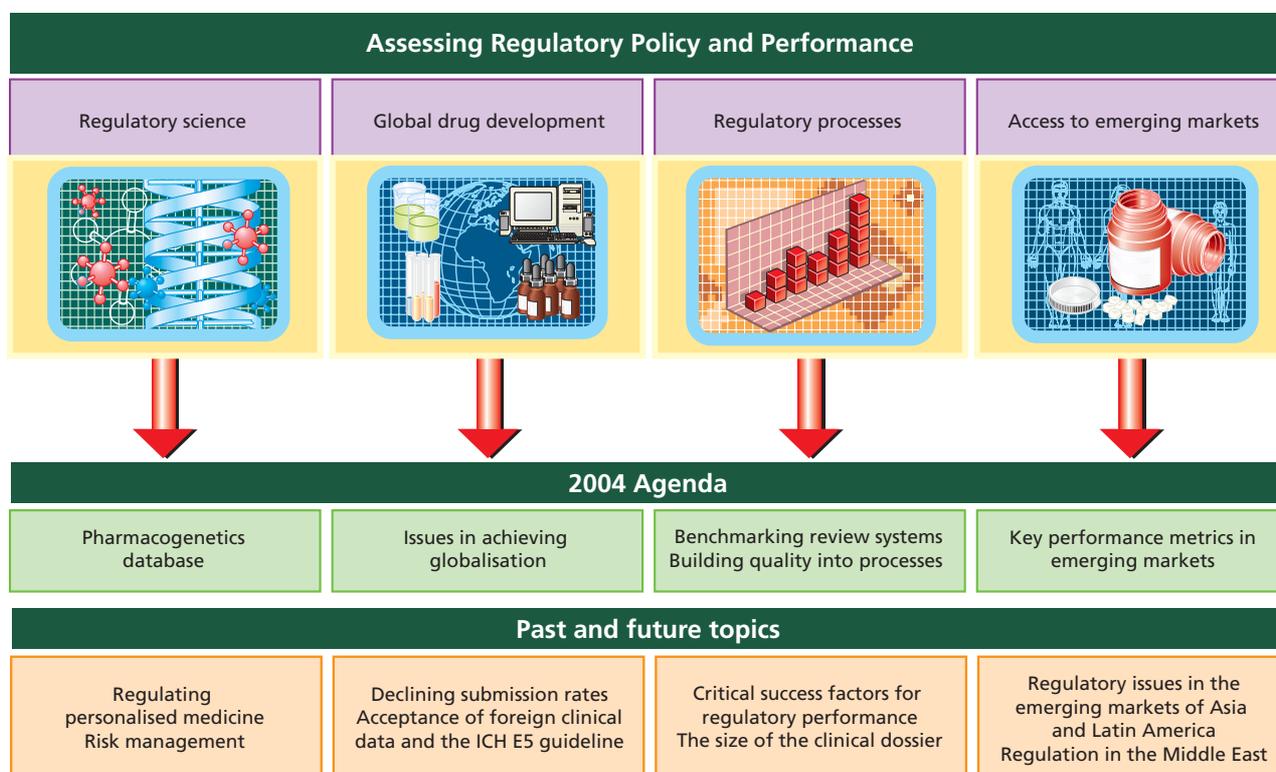
The requirements for registration and CE marking for laboratories and services applies equally to commercial enterprises and to those operating within the health services.

(Points from the discussion)

With appropriate pricing and appropriate targeting of health effects personalised medicine is quite compatible with the concept of 'blockbusters' but this is crucially dependent on whether payers are willing to recognise the concentrated health gain and adjust prices accordingly.

(Adrian Towse)

CMR International Institute for Regulatory Science



Members of the Regulations Advisory Board (2004)

Dr David Jefferys (<i>Chairman</i>), Head of Devices Sector, Medicines and Health products Regulatory Agency (MHRA)	UK
Prof. Gunnar Alván, Director General, Medical Products Agency	Sweden
Dr Leonie Hunt, Director Drug Safety and Evaluation Branch, Therapeutic Goods Administration	Australia
Dr John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration	USA
Dr Murray Lumpkin, Principal Associate Commissioner, Food & Drug Administration	USA
Thomas Lönngren, Executive Director, European Agency for the Evaluation of Medicinal Products, (EMA)	EU
Dr Milan Smíd, Director, State Institute for Drug Control	Czech Republic
Dr Robert Peterson, Director General, Therapeutic Products Directorate, Health Canada	Canada
Prof. Samuel Vožeh, Head of Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic	Switzerland
Dr Graham Burton, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, Celgene Corporation	USA
Dr George Butler, Senior Vice President Worldwide Regulatory Affairs, AstraZeneca Pharmaceuticals	USA
Dr Tim Fransen, Vice President of Global Regulatory Affairs, Lilly Research Laboratories	USA
Dr Stewart Geary, Director Medical Regulatory Affairs and Pharmacovigilance, Eisai Co. Ltd	Japan
Dr Bonnie Goldmann, Senior Vice President, Global Strategic Regulatory Development, Merck Research Laboratories, USA	USA
Dr Paul Huckle, Senior Vice President, European Regulatory Affairs, GlaxoSmithKline	UK
Prof. Stuart Walker, President and Founder of CMR International	UK

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