

R&D Briefing

Pharmacogenetics and Pharmacogenomics in Drug Development



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Survey on

The Integration of Pharmacogenetic and Pharmacogenomic Techniques during Drug Development

Key points	1
Background	2
Company strategy and practice	3
Biological samples, subject selection and profiling	4
Drivers, benefits and hurdles	5
Regulatory advice and submissions	5
Impact on companies and authorities	6
Need for regulatory guidance	7
Issues of concern	8
Can authorities help?	8
Conclusions	9
The next steps	9

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Institute for Regulatory Science**

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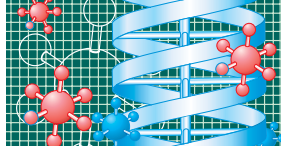
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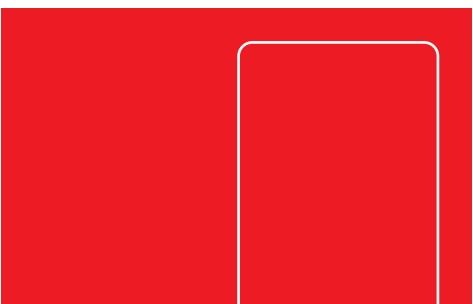
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The Integration of Pharmacogenetic and Pharmacogenomic Techniques during Drug Development

Summarised results of a survey carried out among pharmaceutical companies and regulatory agencies


Key points




Pharmacogenetic (PGt) and pharmacogenomic (PGx) technologies are being applied at some stage during drug development by all 17 pharmaceutical companies that participated in the survey. Such studies are predominantly carried out on selected new active substances in order to investigate target polymorphisms, understand the mechanism of action and to stratify patients for pharmacokinetic (PK) and pharmacodynamic (PD) effects. The use of these technologies is important not only for the selection of patients prior to enrolling them in trials but also to profile patients already in trials, in order to identify genotypes or phenotypes.



At the time of the survey, the majority of companies had already submitted investigational new drug/clinical trial applications and new drug applications that included some PGt and PGx data, to regulatory authorities. These were predominantly submissions to the FDA but also included the EMEA and MHLW. Less than half of those that participated in the study, however, had discussed the use of the techniques with an authority during drug development.



A major driver for industry to utilise PGt and PGx techniques is the need to reduce development times and costs, but there is also a belief that this approach will identify new targets to increase productivity and expand pipelines. For the authorities, the drivers to embrace the new technologies include the promise that these will improve the rationale for medicinal use in terms of indication, dosing and safety management, as well as the demands of industry and patients themselves. Drivers for the healthcare environment are the demand for improved cost-effectiveness and increased drug safety with improved quality, clinical benefit and benefit/risk ratios.



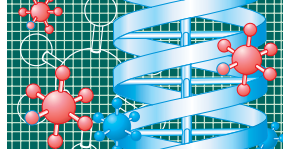
Although the development of regulatory guidance to cover the new sciences is regarded as inevitable, both industry and regulatory authorities expressed concern that premature implementation of guidelines, in the absence of adequate experience and actual case studies, could be detrimental to progress.

Definitions and terminology

For the purpose of this study the definitions used were those outlined in the EMEA Position Paper on Terminology in Pharmacogenetics (EMEA/CPMP/3070/01).

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.



Background



The right drug for the right patient at the right dose and at the right time is the great promise of pharmacogenomics

Pharmacogenomics is the science of understanding the correlation of an individual’s genetic make-up to his or her response to drug treatment. This new science is expected to have a great impact on drug discovery and ultimately help to increase the output of the industry, which is currently suffering from a shortfall of new medicines reaching the market.

Pharmacogenomics is being driven by the need for faster innovation, more effectively designed clinical trials that are better able to predict outcomes, and the need to reduce R&D costs. Another major driver is the potential role of pharmacogenomics in reducing the number of adverse drug reactions, that have been estimated, in the USA, as afflicting over 2 million hospitalised patients annually¹.

Whilst a number of organisations and scientific societies are looking at how the industry should integrate these new technologies into drug development, from discovery

through to economics, little work has been carried out, to date, to address the regulatory aspects and expectations.

CMR Institute study

Companies have already started to include data generated from these technologies in regulatory submissions although discussion of the regulatory implications are at a relatively early stage. A paper by Lesko and Woodcock (2002)² raises a number of issues from a regulatory perspective in pharmacogenomic guided drug development.

In order to study the regulatory issues in more detail the CMR International Institute for Regulatory Science carried out a survey among multinational companies and regulatory authorities, in 2003. The main objective was to establish the *status quo* with respect to the use of these new technologies and obtain views and opinions on the hurdles and issues that are expected to arise with the implementation of these technologies, as well as the perceived benefits.

All 35 pharmaceutical companies in membership of the Institute, and

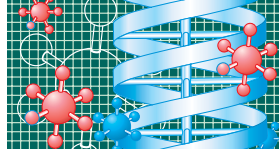
13 regulatory authorities were invited to participate in the study and responses were received from over 60%. In addition to the 9 authorities and 17 companies that were able to provide data (Table 1), there were four companies who responded that they were not sufficiently active in the area of pharmacogenomics and genetics to contribute to the survey at the time.

Preliminary results of the study were presented at the CMR International Institute Workshop on Regulating Personalised Medicines, April 2003. The workshop brought together key experts from industry and regulatory authorities to discuss and debate the current and future challenges in regulating medicines that are ‘personalised’ to individuals’ genetic profiles. Along with the survey results, the workshop provided an opportunity to establish current experience in using pharmacogenetic and pharmacogenomic techniques during drug development and to share and discuss the challenges faced by the regulators and the regulated³

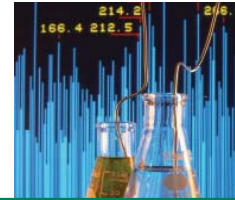
Highlights from the workshop are published in R&D Briefing No 39⁴.

Study participants		
Companies		Authorities
AstraZeneca	Merck, Sharpe & Dohme	Australia, Therapeutic Goods Agency
Aventis	Millennium	Canada, Health Canada
Bayer	Novo Nordisk	EU, European Medicines Evaluation Agency
Bristol-Myers Squibb	NV Organon	France, AFSSAPE
Eisai	Pfizer	Japan, Ministry of Health, Labour and Welfare
GlaxoSmithKline	Roche	Singapore, Health Sciences Authority
Johnson & Johnson	Schering Plough	Sweden, Medical Products Agency
Kyowa Hakko	Wyeth	Switzerland, Swissmedic
Lilly		US, Food and Drug Administration

Table 1



Company strategy and practice



Companies were asked about the extent to which they were applying PGt and PGx techniques, the type of products involved, and the primary objectives.

All companies that provided data for the study indicated that they were applying both PGt and PGx technologies at some stage in drug development. Although a small number were applying PGt techniques to all new active substances (NASs), most were only using them selectively according to the type of product. The techniques were applied less frequently for products that have already been approved for marketing (Figure 1).

Figure 2 gives the main reasons for applying PGt and PGx techniques, according to the clinical phase of development.

Seven companies reported that they were applying the new technologies to understand mechanisms of action at all phases. In general, however, the technologies were applied less frequently in Phase III and even less so in Phase IV.

In the early phases, the technologies are most frequently applied to investigate target polymorphism and to stratify patients for pharma-cokinetic (PK) and pharmacodynamic (PD) effects. In Phase II stratification of patients for response, becomes one of the major drivers.

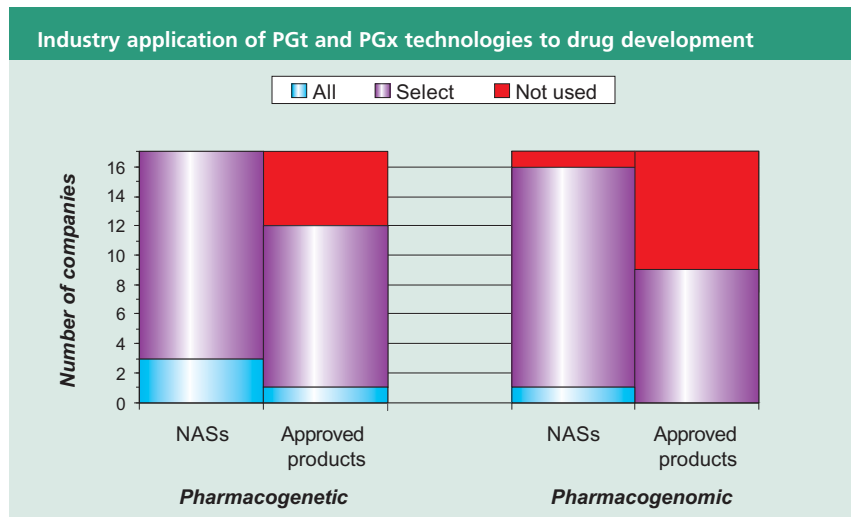


Figure 1

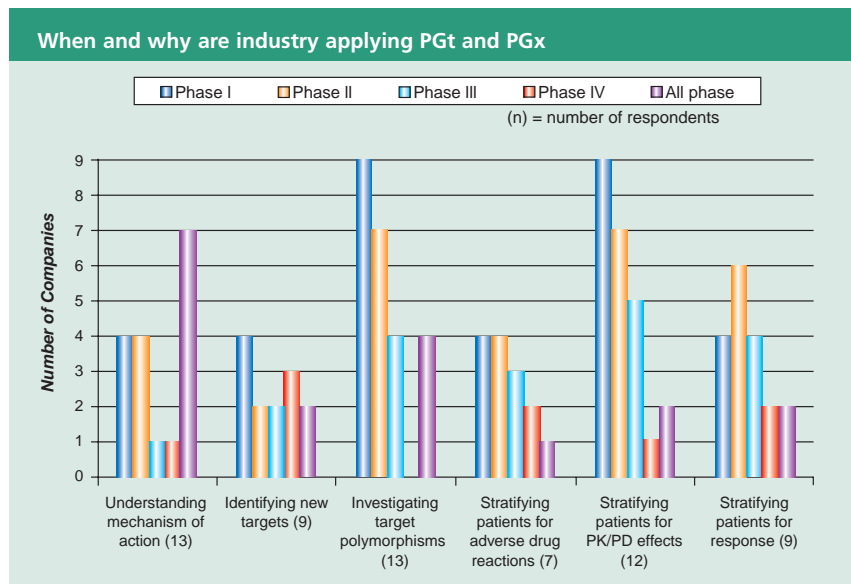
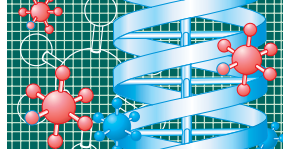


Figure 2



Biological samples, subject selection and profiling



Companies were asked about their normal practices for collecting and storing samples. Of the fifteen companies reporting that they routinely collected biological samples for genetic testing, 14 store samples for the long term, i.e., longer than a year after the study. Samples are collected from both healthy volunteers and clinical trial patients. The banked samples are mostly stored at company owned facilities (n =11), although commercial storage facilities (n = 6) and university sites (n=3) are also used, as part of a collaboration.

Samples are used to select patients for enrolling in trials and/or to profile patients in order to determine their genotype and phenotype, and to obtain information that might provide further insight into clinical trial results.

Companies were asked to give their rationale for selecting and profiling subjects during development from Phase I through to IV and whether or not the reason(s) apply to all NASs or those selected on a case by case basis. All companies indicated that they were taking a case by case approach to selecting and profiling patients. The data in Figure 3 show that patients are most commonly selected for Phase I trials to identify PK effects. At Phase II, in addition to PK effects, they are also selected to identify those at risk of an adverse reaction. Few companies were selecting subjects, using these techniques, to enrol in Phase III trials and none were doing so for Phase IV studies.

The data on profiling patients in clinical trials (Figure 4) indicated that PGt and PGx techniques are used more frequently than for the purpose of subject selection, particularly during Phase II, and for a wider variety of reasons.

The most common reason for profiling patients is, however, the

same as for subject selection – to identify subject with appropriate PK effects and targets, i.e., those patients who are most likely to respond to treatment. In general, there is more patient profiling than stratification, during the later phases (III and IV).

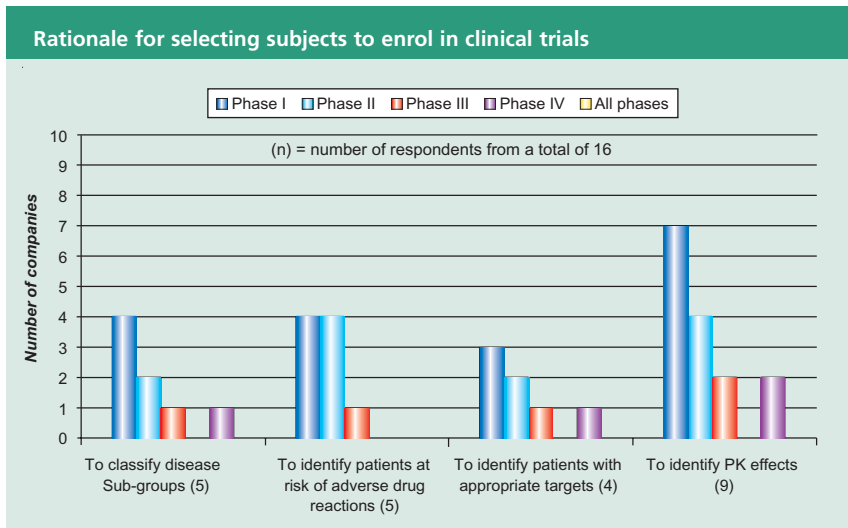


Figure 3

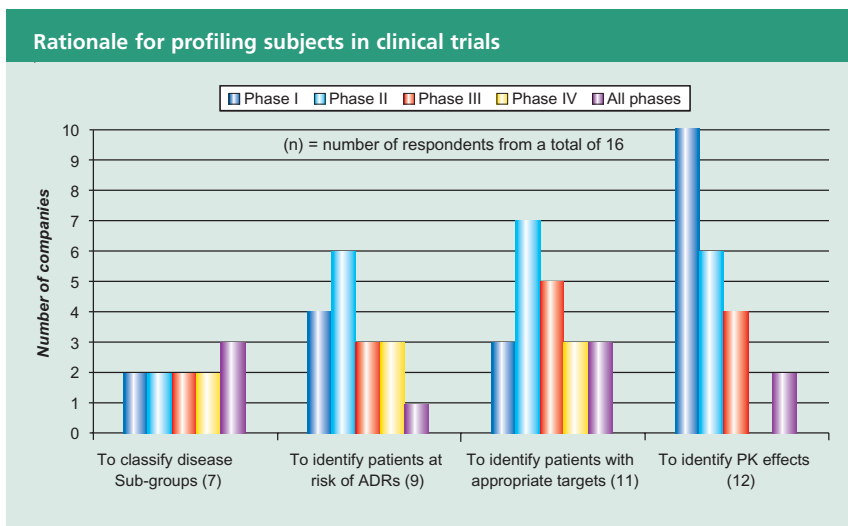
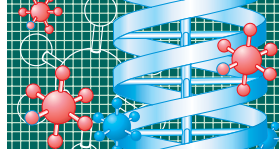


Figure 4



Drivers, benefits and hurdles



Regulatory advice and submissions

Although this new science is still in its infancy, nine of the companies in the survey had experience of submitting applications to the authorities that included PGt and PGx data:

- PGt data had been included in 4 Investigational New Drug (IND), 5 Clinical trial (CT) and 4 New Drug Applications (NDA)
- PGx data had been included in 4 INDs, 4 CT applications and 1 NDA

Less than half the companies surveyed (6), however, had held discussions with a regulatory authority during drug development, the FDA being the predominantly cited authority. The basis of these discussions included:

- Drug metabolising enzyme status
- Improving benefit/risk ratios
- Improving the understanding of clinical results
- Data quality and integrity
- The application and validation of pharmacogenomic technologies

Companies and authorities were asked to describe what they believe to be the factors driving the integration of pharmacogenetic and/or pharmacogenomic technologies into drug development. They were also asked what benefits they believe these new technologies will bring as well as the hurdles they expect in implementing them.

The responses are summarised in Tables 2-4.

Drivers for integrating pharmacogenetics and/or pharmacogenomics

- Need to decrease development times and costs
- Optimisation of healthcare costs leading to improved cost-effectiveness
- To identify new targets to increase productivity & expand pipelines
- Increase targeted therapies
- Improve rationale for medicine use – accurate indication, dosing & safety management
- To remain competitive
- Meet demands of authorities, industry & patients for safer & more beneficial drugs

Table 2

Benefits of integrating pharmacogenetics and/or pharmacogenomics

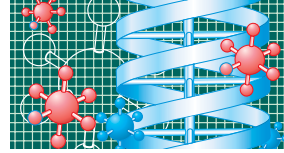
- Improved success rates, decision making, benefit/risk ratios and disease management
- Increase safety and efficacy which in turn will decrease adverse events and improve targeting
- Improved clinical trials – smaller, shorter and less expensive
- Develop more competitive and differentiated products – premium prices for refined products
- Improved understanding of therapies – ability to refine indications, dosing and condition(s) of medicine use, i.e. better diagnosis and treatment
- Decreased costs for all stakeholders as a result of the ability to minimise the number of adverse events and failed drugs, reduce medicine trial and error and avoid treating non-responders

Table 3

Hurdles to integrating pharmacogenetics and/or pharmacogenomics

- Lack of experience, understanding and expertise and the consequent need for education
- Diagnostic tests – difficulties in marketing products associated with tests: supply logistics, reimbursement, competitive advantages, co-development; test validation, regulatory acceptance, availability and cost
- Defining level of validation required in generating data and its applicability to the wider population including the "off label" population
- Application, interpretation and management of the techniques used and data generated
- Need for change in infrastructure for development, clinical setting and commercial environment
- Public perception and ethical issues
- Initial set-up costs
- Market fragmentation which may also create new orphan drugs
- Impact on labelling and prescribing
- Lack of regulatory guidance

Table 4



Impact on companies and authorities



Impact on companies

The majority of companies believe pharmacogenetic and pharmacogenomic techniques have already increased their financial costs and human resources but have had no effect on their development times or success rates in Phases I to III (Figure 5). Asked to predict developments in ten years time, however, most companies believed

that these new technologies would improve benefit/risk decisions. This, in turn, would reduce success rates at Phase I, with compounds that are unable to show robust safety and efficacy being terminated earlier in development, leading to increased success rates at Phases II and III.

Perhaps as a consequence of these expectations, approximately half of the companies believe development times will decrease although human resources are expected to increase.

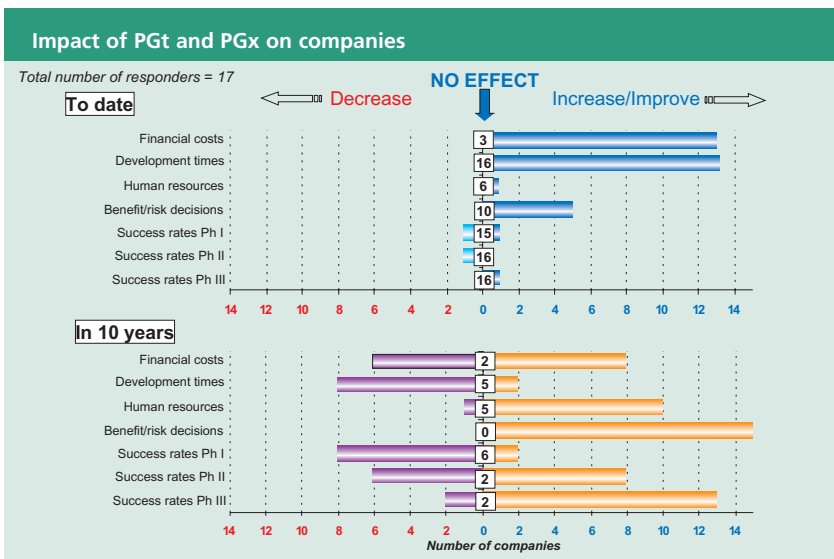


Figure 5

Impact on authorities

By contrast, regulatory authorities have not yet seen a significant impact on their financial costs or human resources as a result of the new technologies, nor have related requests from companies for scientific advice increased. (Figure 6).

As yet, there has been no impact on regulatory review times and authorities do not believe that this will change over the next ten years.

The only impact seen to date, by just under half of the authorities, is improved benefit/risk decisions which are expected to become more widespread in the future. As these techniques become more commonplace over the next decade, however, authorities are expecting their financial costs, human resources and requests for advice from companies to increase.

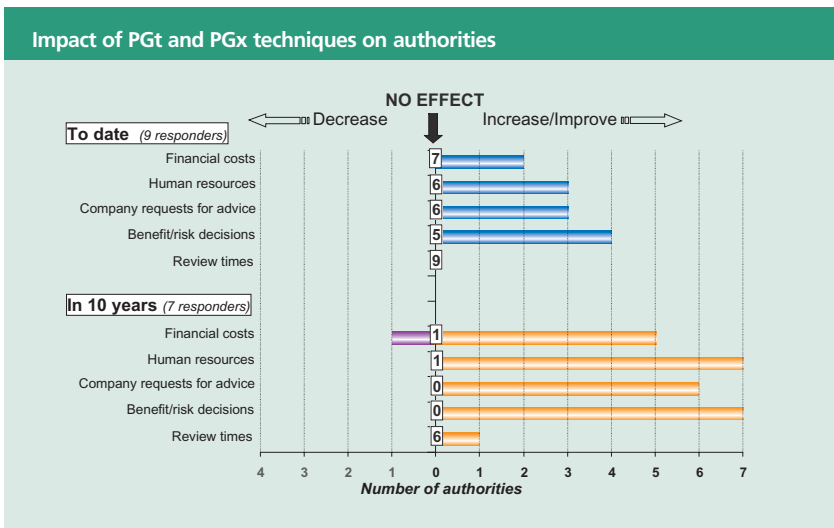
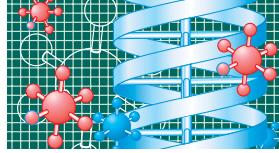


Figure 6



Need for Regulatory Guidance

The study determined whether companies and authorities believed there was an immediate need for regulatory guidance to be developed for the:

- Use of pharmacogenomics and pharmacogenetics during drug development;
- Inclusion of data generated from these technologies in regulatory submissions.

The majority of companies (11) and three authorities (EMA, Health Authority Singapore, Health Canada) believed there was an immediate need for regulatory guidance to be developed in the first category.

The majority of authorities (6) and six companies, however, disagreed. Six of the authorities and just

under half of the companies (7) were of the view that there was no immediate necessity for the second category (guidance on the inclusion of PGx and PGt data in regulatory submissions).

Ten companies felt such guidance was needed as well as the same three authorities that supported the need for guidance related to drug development.

Overall, there were nine companies and three authorities that believed there was an immediate need to develop both types of guidance.

The companies that believe it would be premature to draw up guidelines feel that the technologies and applications are in their

infancy and experience is currently too limited. They felt it would be better to wait for the science to become better defined and clarified. Industry and regulators should adopt a collaborative approach with continuous dialogue and develop guidance in a timely manner.

The reasons given by authorities for not immediately developing guidance also centre on the lack of experience that exists to date, and concerns that premature guidelines may stifle innovation. Using experience from case studies will facilitate the development of guidance that has scientific justification and rationale.

Preferred approaches to developing guidance		
Options (not mutually exclusive)	Preference	
	Companies	Authorities
General guidance	13	7
Case by case guidance	10	3
Definitive guidance	2	1
More interaction across industry	13	4
More interaction across authorities	15	7
More interaction between industry and authorities	16	6

Table 5

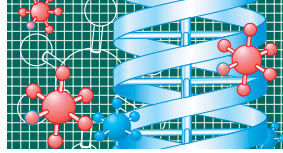
The survey indicated that the majority of respondents would like to see greater interaction across and between industry and authorities in order to develop general regulatory guidance on the utilisation of pharmacogenomic and pharmacogenetic techniques during drug development and the subsequent inclusion of data generated from these technologies in regulatory submissions.

Problem areas include:

- Lack of available data and standards
- Belief that the appropriate infrastructure is not yet in place
- Lack of consensus on how data generated using these technologies should be interpreted and translated into advice and recommendations

- Insufficient examples and data available to develop this consensus

Looking to the future, there is belief that hurdles will become more centred around ethical issues and constraints as well as outstanding differences that still remain in regulatory requirements across regions.



Issues of concern



Companies and authorities were asked to identify the three key regulatory issues of greatest concern when utilising PGt and PGx techniques in drug development. The common and differing views are summarised in Table 6.

Key issues of concern
<p><i>For both industry and authorities</i></p> <ul style="list-style-type: none"> ■ Diagnostic tests: Potential need to develop these in parallel with new drugs and associated marketing logistics; their availability, validation and utility in clinical settings; their accuracy, validity, reliability, stability, sensitivity, specificity, quality assurance and impact on labelling ■ Data management: How data will be interpreted, reviewed and used for decision making, agreement on when and what to submit to authorities; how findings of uncertain significance will be handled; data reliability and verification <p><i>For industry</i></p> <ul style="list-style-type: none"> ■ Increased costs incurred in obtaining and analysing data ■ Labelling implications, particularly where claims are based on data generated from technologies ■ Patient privacy and confidentiality: Auditing of anonymised data; ownership rights <p><i>For authorities</i></p> <ul style="list-style-type: none"> ■ Reviewer competencies: Lack of experience, knowledge and understanding; need for training ■ Extrapolation to wider population: Ethical discriminatory issues if data only generated from responders creating limited exposure; uncertain outcomes if used by "off label" population

Table 6

Can the authorities help move the science forward?

Both companies and authorities were asked how they believed regulators could help companies to make progress in the integration of PGx and PGt into the development process for future medicines.

Both regulators and industry were agreed that the priorities were:

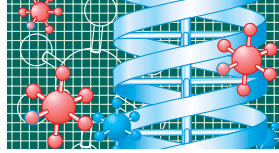
- Continuous open dialogue at forums, workshops and company meetings
- Making the best use of opportunities for scientific advice from regulators and starting such discussions at and early stage

- Working in collaboration with industry on the development of guidance on appropriate practices and standards

The suggestions from industry on the role that the authorities could play in furthering use of the new technologies also included the following:

- A collaborative approach to utility, interpretation, evaluation and validation of technologies
- Consideration of the acceptance of surrogate markers
- Acceptance of the nature of exploratory studies

- Flexibility in approving medicines for unmet medical need in the absence of data for non-responders, provided suitable labeling is agreed
- A proponent for sample collections for future research
- A partner in educational programmes for all parties including industry, regulators and the public



Conclusions



Recent technological advances in science mean that the vision of developing 'the right drug at the right dose for the right patient' is becoming a reality. The integration of pharmacogenetics and pharmacogenomics into drug development is, however, an evolving science that is still in its infancy. The experience, case histories and data generated from these new technologies are limited. There is a need to develop expertise, knowledge and understanding across industry and regulatory authorities before consensus can be reached on ways forward that will maximise the potential of these new developments and not stifle innovation. A collaborative approach is essential. This collaboration must incorporate all the parties involved, now and in the future. These include academia, pharmacists, physicians and the developers and manufacturers of the essential diagnostic tools. Those who fund

healthcare services and the ultimate users, the patients and the public must also be included as key players in the debate.

The next steps

This study was conducted by the CMR International Institute for Regulatory Science in preparation for its Workshop on Regulating Personalised Medicine^{3,4}. It was recognised that this was a preliminary study carried out among companies and regulatory agencies at a relatively early stage in the development and implementation of the new technologies.

When the subject of a follow-up study was discussed at the Institute Workshop it was agreed that, it would be valuable to conduct a similar survey at some point in the future in order to measure the growth of pharmacogenomics and pharmacogenetics and assess whether there had been a change in current opinion and perceptions of 'personalised' medicines. In the meantime, however, the

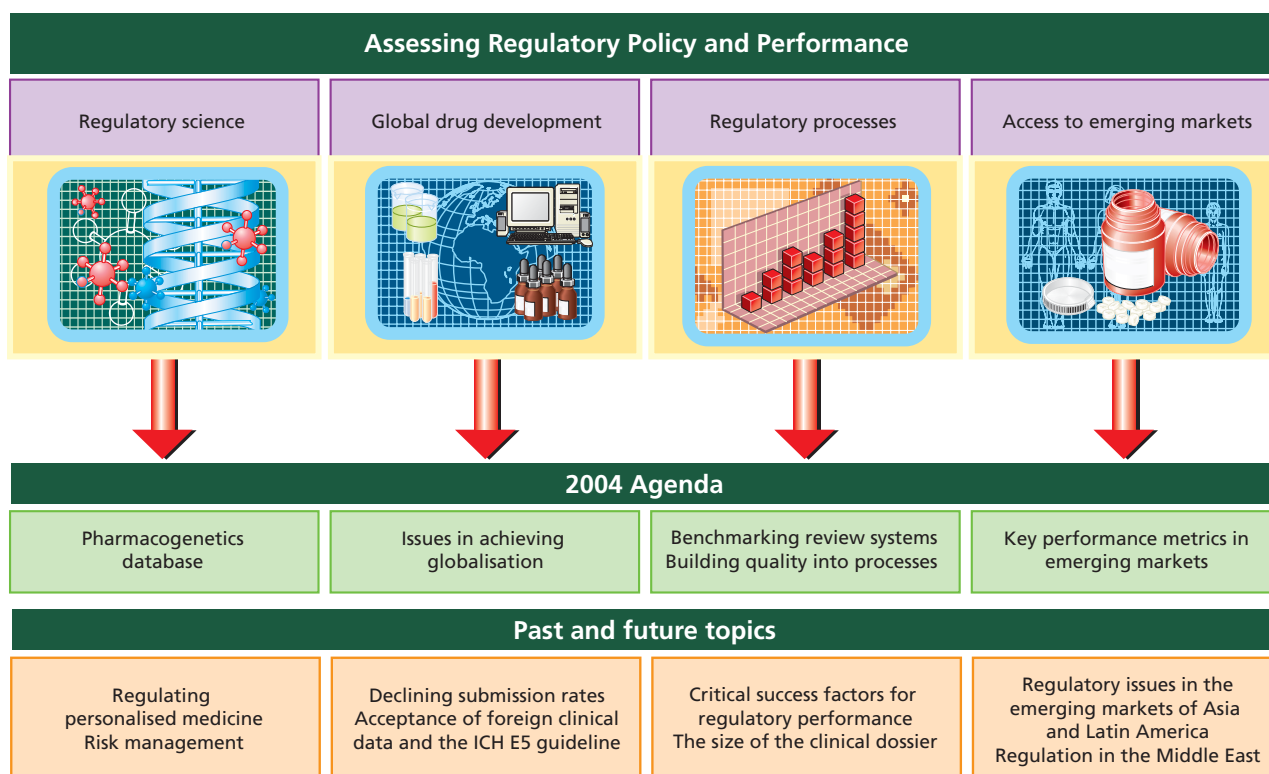
Workshop recommended that the CMR International Institute should set up a prospective database of information on the use of PGx and PGt in drug development. The database would:

- 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.

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