



Optimizing stratified medicines R&D: addressing scientific and economic issues

Report of a meeting organised by the Academy of Medical Sciences,
Roche and GE Healthcare.

The Academy of Medical Sciences

The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. Our Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

The Academy of Medical Sciences FORUM

The FORUM is an active network of scientists from industrial companies and academia. It currently focuses on the pharmaceutical, biotechnology, medical engineering, medical IT, and health product sectors with representation from relevant trade organisations, Government departments, Research Councils, and other major research sponsors. Medico-legal and venture capital firms are also included.

The FORUM promotes interaction between industrial and academic biomedical scientists and engineers, and other groups committed to improvements in healthcare through research.

Acknowledgements

This report is published by the Academy of Medical Sciences and has been endorsed by its Officers and Council. The Academy warmly thanks the speakers, session chairmen and delegates for their participation. Our thanks also to Dr Robin Fears for writing this meeting report.

The Academy is grateful to the generous support of Roche and GE Healthcare in co-organising this meeting.



www.roche.com

GE Healthcare



www.gehealthcare.com



Optimizing stratified medicines R&D: addressing scientific and economic issues

Report of a meeting organised by the Academy of Medical Sciences,
Roche and GE Healthcare.

Contents

Summary	3
Introduction	4
Economic issues: creating and rewarding value	5
Research and development issues: processes and implications	8
Proposed reforms to enhance innovation and development in the UK	11
Commercialisation and access issues	13
Reforms to drug discovery and development	15
Conclusions from the meeting	18
Related work by the Academy of Medical Sciences	19
Annex I: Meeting programme	20
Annex II: Meeting Delegates	22

Summary

The Academy of Medical Sciences co-organised a meeting with Roche and GE Healthcare to explore issues associated with the introduction of stratified medicines – the better targeting of interventions to well-defined sub-groups of patients. This targeting should enhance patient care by the development and use of safer and more effective drugs but there are obstacles within the regulatory and pricing frameworks, which do not yet provide the necessary flexibility to assess healthcare value and to reward the innovator.

The meeting shared perspectives from economists, clinical researchers and policy-makers to determine the options for taking forward stratified medicines research and development. The UK is well placed to capitalise on current strengths in evaluation (National Institute of Health and Clinical Excellence) and on the developments in patient informatics databases (Connecting for Health) as a research resource to evaluate drug responsiveness, and there are new proposals for the organisation of biomedical research and development with a focus on translational medicine and regulatory reform (the Cooksey Review recommendations).

Speakers addressed topics across a broad front:

- Economic issues, based on models for creating and rewarding value.
- Research and development issues for the pharmaceutical sector (opportunities for validating and using biomarkers and for stratification throughout the product lifecycle) and the diagnostic sector (new technologies and business models).
- Options for regulatory reform, in particular the feasibility of conditional licensing – allowing new drugs in NHS priority areas to be made available to patients following preliminary safety studies and proof of efficacy.
- Commercialisation and health services delivery issues, including the lessons learned from the first opportunities to stratify patient groups.

Drawing on evidence from case studies and the analysis of perspectives from the UK and USA, discussion groups sought practical solutions for the reform of regulation of drug development and the encouragement of faster uptake of proven therapeutic innovation together with appropriate capture of the changing value of stratified medicine products. There was consensus that stratification is desirable for patients and healthcare systems and for companies, but there are considerable challenges:

- There is often a barrier in defining stratification prior to drug registration because of the difficulty in developing a therapeutic and diagnostic simultaneously.
- There may be relatively little incentive for diagnostic companies because of their problems in protecting intellectual property and the cost of demonstrating clinical utility.
- There may be relatively little incentive for pharmaceutical companies in post-approval stratification because their current commercial environment lacks pricing flexibility.
- The research infrastructure with which to assess clinical utility does not always exist.

Therefore, it is concluded as essential, for societal as well as company benefit, to devise new incentives for pharmaceutical companies (pricing flexibility linked to demonstrable value) and diagnostic companies (patent protection and support for clinical development programmes). Providing new incentives would complement and facilitate the opportunities for public-private research partnership to establish clinical utility and the new approaches to regulatory dialogue. In particular, the Cooksey Review proposal on conditional approval may provide one means to become more flexible in assessing the value of stratified medicine.

Introduction

Health risks, disease course and therapy responses that can be well classified at the population level often vary considerably among individuals. Recent technological breakthroughs offer the prospect to enhance patient care with safer and more effective drugs, delivered with greater certainty of success to those in need. It is anticipated that better understanding of molecular variation in disease will lead to defined sub-types, allowing determination of which course of action is most appropriate for patients within these sub-types. This is stratified medicine.

Reduction in uncertainty for healthcare interventions can add value in many ways but current systems that reward innovators do not typically offer the flexibility needed to assess the magnitude of increases in value and the means to appropriately partition the rewards that are expected to flow from stratified medicines. The UK represents a very important test-bed for ascertaining how best to structure valuation processes and incentives so as to optimise investment in stratified medicines research and development:

1. NICE is a well-defined system for assessing product cost-effectiveness at launch and thus defining potential value capture.
2. The NHS Connecting for Health initiative is creating a patient informatics resource that may enable post-launch drug responder research.
3. The recent Cooksey review provides detailed analysis of the current strengths and weaknesses of UK biomedical research and development and proposes a new model for pharmaceutical innovation through 'conditional licensing'.

In order to consider further the opportunities and barriers in this area, the Academy of Medical Sciences, Roche and GE Healthcare co-organised a meeting to share perspectives from economists, clinical researchers and policy-makers in the public and private sectors. Drawing on experience from the UK and USA, the meeting attendees sought to test some of the basic assumptions on rewarding value and to help identify the strategic options for taking forward stratified medicines research and development.

In his introductory overview, **Dr Scott Gottlieb** (American Enterprise Institute), observed that healthcare systems do not currently use all the information that is available to them, for example from biomarkers and diagnostic scans. Although part of the reason might be the uncertainty of an emerging science, the main barriers are judged to be political, regulatory and economic, including the way that resources are allocated and managed. The reimbursement environment has been generally resistant to paying for stratification and the business model for stratifying patients is not yet well developed. A key challenge for policy-makers is how to ensure that healthcare decision-making makes better use of all of the available information and this challenge pervaded much of the discussion during the meeting.

Economic issues: creating and rewarding value

Dr Louis Garrison (University of Washington) began the presentations by addressing the economics of stratification based on a model of value creation and capture for combinations of (biomarker-based) diagnostic and therapeutic agents. Such combinations are expected increasingly to inform treatment selection by predicting the safety and efficacy achievable in specific sub-groups of patients. Linking innovative diagnostic and therapeutic agents may create societal value by reducing the overall incidence of adverse events (by excluding non-responders from the pool of users) and, as a consequence of reducing the uncertainty about a favourable outcome, by increasing adoption and compliance by responders. However, pharmaceutical manufacturers have limited incentive to invest in diagnostics that may restrict the size of their market. Moreover, the current business models are very different for manufacturers of prescription pharmaceuticals (based on high margin/high risk, intellectual property (IP)-protected, and assumptions of blockbuster financing) and diagnostics (based on low margins, platform-based technology, and assumptions of high volume).

Companies have little latitude to increase price after a drug is marketed – while economists assert that price is the best indicator of value in a well-functioning market, prices are prohibited from changing without government approval in many European countries and even face substantial inflexibility or, at least, inertia in the US's more open market. Strategies for improving payment systems for drugs need to pay attention not only to maximising the benefits from the current drug budget, but also to look to the future, considering the incentive effects on the development of new drugs – a concept of dynamic efficiency rather than static efficiency.

A simple theoretical model was used – considering multiple perspectives, including the manufacturer, the payer, and the patient

perspective – to characterise a range of scenarios and calculate the potential added value generated by combining a therapeutic with diagnostic test; and to identify who can capture this value and what incentives are thereby created to develop and use the linked product. The scenarios were constructed according to whether the diagnostic appears on the market at the same time as the therapeutic, or subsequently, and to the degree of flexibility in pricing allowed. For example, if the therapeutic is already on the market when the diagnostic enters then the pharmaceutical manufacturer suffers reduced return on investment if there is no pricing flexibility but gains, if able to raise prices (assuming strong IP protection). If the therapeutic and diagnostic are launched together then the relative gain by each depends on whether one or both have flexible pricing (if both are flexible then competitive market conditions will be a key determinant)¹.

In summary, introduction of value-based reimbursement and pricing could provide major incentives to therapeutic and diagnostic manufacturers. The observed dependency in the theoretical model of incentives on the flexibility of pricing and reimbursement systems and IP protection, as well as on the timing of market entry, has implications for policy-makers in encouraging stratified medicine.

In discussion, consideration of the scenarios was extended to include the case where the therapeutic is a generic product – in this case it is still possible for the diagnostic manufacturer to create value although healthcare services may prefer to use other patient sub-group targeting/drug titration strategies (discussed in subsequent presentations). It was also noted that the theoretical construct may need to be more sophisticated if it is to be generalisable. For example, the assumed dichotomous drug response may actually be a continuum of efficacy responses (and may be accompanied by adverse events) and it may also be necessary to

1 The scenarios are discussed in detail in Garrison LP & Austin MJF (2007). *The economics of personalized medicine: a model of incentives for value creation and capture*. Drug Information Journal **41**, 501-509.

model the issues for greater market penetration associated with reduction in uncertainty. Manufacturer behaviour is also highly relevant in establishing who captures value. On the basis of their present business culture, diagnostic companies tend not to be risk takers so it is those companies involved in developing both diagnostics and therapeutics who are most likely to respond to the incentives to capture value in parallel development. The position for diagnostic companies will only change if the current business model (and reimbursement), based on the diagnostic as commodity, changes to recognise the value that the test brings for the patient.

Professor Adrian Towse (Office of Health Economics) presented a case study of value creation and capture in osteoporosis, a high disease burden in the UK (nearly one million patients with a current annual cost of treatment of fracture of £1,800 million). The main therapy is the bisphosphonates; several biomarkers could be used in principle to direct diagnosis and treatment but are not currently used in practice. The case study analysis compared QALYs (Quality Adjusted Life Years) gained on secondary intervention treatment according to the current guidance by NICE (issued in 2005 and based on measurement of bone mineral density and the identification of clinical risk factors) or by the better targeting of bisphosphonates by using bone formation and resorption markers to identify patients at most risk of fracture. The comparison shows that using biomarkers to select only those most at risk improves the cost-effectiveness of bisphosphonates in certain population sub-groups (for example, those aged 60) by comparison with the NICE base case scenario. This increased social value accruing from targeted treatment of those patient cohorts excluded by the NICE guidance is then available for capture by either the therapeutic or diagnostic manufacturer. Paradoxically, using biomarkers to target the smaller subset of older patients (aged 80) reduces the net value for the whole cohort at that age because

treatment is already cost-effective according to the NICE guidance. Therefore, targeting of interventions will need to vary subject to the characteristics of the population to be treated. In this case study the impact, of targeting on value creation also depends on the patent status of the therapeutic, reinforcing the prediction from the theoretical model used by Dr Garrison. Recent NICE guidance (2007) on the leading generic bisphosphonate, Alendronate, now recommends secondary prevention in all post-menopausal women, irrespective of age (and primary prevention in older women). Because use of generics reduces treatment costs and improves baseline cost-effectiveness, there is less incentive for diagnostic manufacturers to explore biomarkers – who then should do this research?

Discussants raised several other practical issues for the interpretation of economic models and the generalisability of case study analysis. If repeat testing improves compliance (because of a demonstrable response to the therapeutic), does improved compliance change the value gained? How should biomarker assay quality (in particular, the propensity to yield false positive or negative results) be taken account of in the sensitivity analysis for the determination of impact and hence value created? Other points raised in discussion became recurrent themes in the meeting. What are the implications for IP protection? For example, can coupling diagnostic with therapeutic extend the patent life of the latter (customarily, use patents are deemed to be less helpful than the standard composition of matter patents)? At what point should independent therapeutic and diagnostic companies discuss how to maximise the capture of value? The consensus view is as early as possible. What evidence is needed to demonstrate clinical utility as well as analytical validity? Should clinical utility be required in patent applications and who pays for the framework of extended evaluation?

Dr John Calfee (American Enterprise Institute) tackled the problem of pharmaceutical

research and development incentives in a single-price market with particular reference to the need to reward the different value that a therapeutic may demonstrate in stratified patient cohorts, different clinical indications or changed circumstances (for example, in drug combination therapy or new delivery systems). Some of these alternative uses may occur simultaneously, providing great value to patients and healthcare systems, but may only be revealed by costly new research and development to demonstrate the 'high value' patients, perhaps comparable in complexity and cost to the research and development that supported the initial approval. While examples of dynamic pricing (Norvir, Avastin) can be found, they are relatively rare, even in the US market. There is concern that a single drug price, even if permitted to change over time, may fail to provide reasonable incentive to perform the research necessary to explore new uses.

Case study analysis of the use of VEGF inhibitors for age-related macular degeneration, stimulated by the NIH National Eye Institute direct comparison of Avastin and Lucentis, raises an additional concern - that attempts

to undermine the pricing structure for newer agents endangers the differential incentives for future research and development that might otherwise be possible through dynamic pricing systems. This point aroused controversy in discussion, and for the purposes of this meeting it was agreed important to focus on the issues for the differential pricing strategy in support of stratification, not drug pricing *per se*. There are practical challenges for how healthcare systems manage the different uses of drugs and there is a case to be made for the legitimate responsibility of public authorities in evaluating the comparative impact of different drugs within a class. This is an area requiring early dialogue between company and regulator on value, acknowledging that the difficulties in estimating value (and price) prospectively are compounded by the potential for multiple clinical indications. Discussants also considered the potential merits of other possible approaches to company risk-sharing after launch, for example the linking of price to defined patient outcomes in routine clinical practice, that may yield viable pricing constructs, highly relevant to the subsequent discussion of conditional approval.

Research and development issues: processes and implications

Dr Chris Chamberlain (Roche Products) explored some of the opportunities for achieving enhanced clinical utility through stratification within the multiple dimensions of the product lifecycle:

The environment driving biomarker use in drug development

For the company, internal use of biomarkers during the research and development process can resolve uncertainties in drug metabolism and the demonstration of safety and efficacy. After drug launch, biomarker use may help in the stratification of who to treat, as described by previous speakers. Initial research and development attention to biomarkers in pharmacokinetics has expanded following the realisation of their usefulness to inform disease predisposition, detection, prognosis and monitoring.

There is a growing practicality of stratification. Diagnostic technology costs are decreasing, opening up new applications for clinical use. Key technology platforms are already embedded in laboratory medicine and available for new diagnostic applications. There is growing demand from the Regulatory Authorities for stratification.

Using biomarkers across the research and development lifecycle

Potentially, there is wide utility for biomarkers, to understand pathobiology (predicting disease, responsiveness and separating phenotypes); during the drug discovery phase (target identification and validation); in early development (stratifying pharmacokinetics, mechanism of action studies, safety assessment); later development (stratifying pharmacodynamics); and into the marketplace, to inform the continuing capacity to understand the determinants of efficacy and safety.

It is contended that it is relatively straight forward to stratify for efficacy because of the

large cohorts available for analysis with a wide range of phenotypes and with a low risk to patients in false positive results, such that there is strong competitive pressure for pharmaceutical companies to engage in such studies. Stratifying for adverse events is much more demanding because events are rare and there is a high risk to patients in false negative results.

Translating biomarkers into clinical practice

Much is already in place to support the translation of biomarkers into clinical practice – the scientific advances, diagnostic platforms, engagement with regulators. What is still lacking, is access to high quality clinical samples. There is need to build biobanks and there is concomitant need to clarify the relative technical requirements, ethical and operating procedures to collect DNA samples (static collection) or specific metabolites and RNA as a function of time (dynamic collection). While there are already some good sample sources (academic collections, population biobanks, company archives, the EUDRAGENE initiative), there is much more to be done to construct prospective collections for the purpose of monitoring the therapeutic response.

Implications for personalized healthcare

In today's empirically-prescribed mass market, poor therapeutic responses are well described and already there are opportunities for targeting, but personalized healthcare solutions are uncommon. Why is this? A specific illustration was provided later in the meeting for Cytochrome P450 biomarkers. More generally, from the research and development perspective there are likely to be some common themes from the emerging examples of successful personalized healthcare: heterogeneity in the disease and its response to therapy; an unmet medical need, probably in an advanced medical care setting; a risk and cost inherent in taking a 'trial and error' approach to therapy; fundamental knowledge of the disease biology and drug mechanism of action; and, not least,

feasibility in using the research concept to develop a diagnostic.

What then are the barriers to research and development reform for achieving enhanced clinical utility through stratification? There is still much uncertainty on how stratification would affect the return on research and development investment; in addition to the points made by the previous speakers, a more complex product may suffer from slower development. And to reiterate points made previously, how will stratification of a drug in the marketplace be rewarded? Is a flexible pricing option feasible or could research and development funding be obtained by public sponsorship?

These contentious issues for research and development were pursued in general discussion and helped to set the framework for the Breakout Group sessions. It was observed that using biomarkers to create enriched research and development clinical populations might be particularly valuable in phase II to identify responder sub-groups without dilution of the efficacy response signal in a broader population. But, if regulatory approval is based on a small cohort, what are the opportunities for subsequently generalising to a larger population? Can there be sufficient confidence in biomarker results in the relatively small numbers used in Phase II and might this become a greater concern if information based on inappropriate sub-groups or biomarkers is carried through to the product label? It may be preferable not to couple a therapeutic agent with a single biomarker test technology so as to provide flexibility in regulatory discussions, to avoid potential linkage to a test that might be superseded by new technology and to provide a better business model for the pharmaceutical company, engaging with several prospective diagnostic partners. Some pharmaceutical companies remain cautious about the likely impact of biomarkers in developing stratified medicines – mainly because of the perceived difficulty in capturing increased value by higher

prices for targeted therapy and because other companies may be able to appropriate the same information for competitive purposes. This latter point must also be taken into account when considering the options for public investment, public-private partnership and pre-competitive consortia to support fundamental research. There may be particular possibilities for collaborative working on safety biomarkers, if these represent a harder challenge than efficacy biomarkers. One option, at the EU level, is the Innovative Medicines Initiative representing a consortium of companies engaged in pre-competitive research in several therapeutic areas² and in the UK the NHS itself is a research resource that provides a singular opportunity for shared work on safety assessment.

Jens Sorensen (GE Healthcare) reviewed the development and integration of molecular imaging in stratified medicine – non-invasively probing tissue function at the molecular level. Much progress has been made in clarifying the molecular and cellular target criteria (in terms of specificity, accessibility and protein expression level), vector criteria (in terms of affinity and feasibility) and the relative merits of the imaging tools available (PET, SPECT, MRI and optical platforms). There is now a significant volume of research on 18-Fluorodeoxyglucose (FDG) in oncology, particularly in lymphomas, to support treatment stratification, monitoring and prognosis (acting as a gatekeeper for further intervention). There is also much academic work on tumour-specific tracers (for example 11C-5-hydroxytryptophan, a serotonin precursor, for neuroendocrine tumours), but such tracers can be difficult to formulate. An alternative to research on tumour-specific tracers is molecular imaging of the common attributes of many tumour types (for example, the processes of angiogenesis, apoptosis, hypoxia); a case study described the utility of GE-135 in an integrated diagnostic-anti-angiogenic therapeutic approach. Other case studies illustrated the value of transforming older drugs into PET probes

² The Innovative Medicines Initiative launched by the European Commission with the pharmaceutical sector to operate a new public-private partnership tackling the principal bottlenecks currently slowing down pharmaceutical research and development. The Strategic Research Agenda (www.imi-europe.org) covers issues for biomarker prediction of safety and efficacy together with bridging gaps in knowledge management and in education and training.

(for example, F-DOPA as imaging marker for the dopaminergic system) and of using molecular imaging to tackle hitherto intractable clinical challenges, exemplified by GE-067 a diagnostic agent for Alzheimer's Disease, that might also be used to measure treatment outcome in terms of amyloid burden. The clinical benefits that could accrue from such a molecular approach are significant and include: earlier detection of molecular or physiological alterations that could lead to earlier detection and treatment of diseases (with potentially higher cure rates), the ability to monitor therapy which could help in both evaluating and adjusting treatments in real time, and enabling development of novel therapies (as indicated in the FDA's Critical Path Initiative).

Many potentially useful imaging biomarkers already exist in research and some are in development. Research results have been obtained that support the potential utility and benefit of these agents. There are, however, major challenges for the molecular imaging manufacturer in providing the relevant hardware and software as well as the tracer, and in training enough clinicians so as to enable the translation of the technology from specialised centres into clinical practice. Moreover, apart from FDG, the development of tracers is difficult, with particular challenges for synthesis (isotopes may be short-lived), Good Manufacturing Practice (providing microgram amounts), regulatory approval (currently based on therapeutic approval pathways), standardisation, analysis and economic viability, despite progress in creating a Global Imaging Network to facilitate clinical trial standardisation. In summary, although molecular imaging could play a major role in the stratification of patient populations,

widespread use and application of imaging biomarkers depends on finding a way to get them approved and eventually reimbursed. To do so, standardization of manufacturing, image acquisition, and image analysis needs to be combined with creative approaches to labeling and clinical trial design.

The discussion session ranged widely in considering the opportunities and barriers for molecular imaging, and the points of resemblance with therapeutic R&D, including a strong IP protection afforded the in-vivo tracer molecule, which was contrasted with biomarkers used in in-vitro diagnostics where IP may be a challenge if confined to the biomarker and some consider that the patenting strategy for IVD should concentrate more on the intellectual content, linking test with disease. The R&D attrition rate for imaging tracers is probably similar to the pharmaceutical sector, although it is difficult to extrapolate from the much smaller imaging sector. There are utility challenges in linking technical results from imaging to clinically-relevant outcomes, and business model challenges in interacting with the competing therapeutic companies whose compounds may be equally relevant for coupling with the imaging approach to stratify trial populations. Molecular imaging is currently used essentially when all other diagnostic approaches are exhausted. For future projections of cost-effectiveness (and reimbursement potential), it is important to assess the cost of molecular imaging when used as the diagnostic entry point rather than as technology of last resort. However, the current scale of use of imaging is small compared to other diagnostics and the collection of economic data will be laborious.

Proposed reforms to enhance innovation and development in the UK

Professor John Bell PMedSci (Academy of Medical Sciences) introduced the session by describing the terms of reference and outcomes from the Cooksey Review and the early activities of The Office for Strategic Coordination of Health Research (OSCHR), with particular regard to defining and addressing the scope of Translational Medicine. One reform proposed by the Cooksey Review and of particular relevance to the present meeting is conditional licensing - to allow new drugs in NHS priority areas to be made available to NHS patients following preliminary safety studies and proof of efficacy.

Richard Barker (ABPI) discussed the potential impact of the Cooksey Review on stratified medicines from the pharmaceutical industry perspective, based on broad agreement with previous speakers about the general benefits that might accrue from stratified medicines, notwithstanding the challenges for the clinical validation of biomarkers and the current mismatch between the therapeutic and diagnostic company business models.

The Cooksey analysis is judged to be sound, and enticing for pharmaceutical research and development in terms of the prospects for improved collaboration between the private and public research and development sectors, the added value of early dialogue between companies and their customer (NICE) and the principle of fast-tracked conditional regulatory approval. The Cooksey Review proposed focus on national health priorities is more controversial from the pharmaceutical sector perspective, given that companies must fulfil global not local objectives. Further discussion is warranted to resolve some of the other key industry questions about conditional approval – what level of risk will be acceptable in earlier approval (presumably different for different diseases) and what are the implications for product liability, patient consent and patient

information in post-approval trials?

Some in industry will need persuading that the Cooksey model can work when a tendency elsewhere for anti-industry sentiments can make the environment confrontational and less tolerant of risk. If reassurance on the industry concerns is forthcoming, the increased need for post-marketing surveillance following conditional approval may be satisfied in due course by implementation of 'Connecting for Health' but until those informatics systems are established (and applied to research), there is need to continue to extract the maximum value from the General Practice Research Database and the Scottish and Welsh health informatics pharmacovigilance initiatives.

In summary, the Cooksey model provides new opportunities for delivering the benefits of stratified medicines, if the policy imperatives identified by the previous speakers can be addressed: the critical role of pre-competitive public-private partnership (for collecting samples, instituting technology platforms, validating methodologies); the adoption of regulatory tools to facilitate costly therapeutic-diagnostic co-development; the assessment of broadly-defined clinical value that is sufficiently flexible to incorporate evidence generated throughout the product lifecycle; and the reform of pricing and reimbursement systems to recognise that product value can increase as well as decrease.

Further discussion of many of the necessary attributes for a framework for conditional approval provided a range of ideas to inform the subsequent Breakout Group sessions. One other key challenge was identified: if it is agreed that validation of biomarkers is more important than their discovery, who will do this validation work? There is a major continuing role for the HTA programme in validation but programme capacity must be expanded, requiring the training of additional researchers and thought given to devising researcher reward systems based on metrics other than the number of

high-impact publications.

In reviewing the broad range of emerging issues for biomarkers (Box 1), **Professor Munir Pirmohamed** (University of Liverpool) concluded that there can be no single solution to ensuring their discovery, validation and use.

In response to the question, 'who pays?' it is clear that the public sector has a major interest in supporting research, particularly for off-patent drugs but that if there is to be public-private partnership to generate data then it is necessary to be unambiguous about the nature and quality of the evidence required.

Box 1 Commentary on the first day of the meeting: A clinician's perspective

The issues associated with the identification, development and use of biomarkers include:

- What sort of evidence is needed from biomarkers to change treatment?
- How can that evidence be obtained? While randomised controlled trials will be employed for new drug research and development, are observational data sets also valuable and how can biomarker collection be incorporated into publicly-funded trials?
- What are the biobank access and availability issues and how good is the concomitant information on phenotyping?
- Who pays for generating the evidence? Is it desirable and is it possible to move costs from the company to the purchaser (NHS)?
- What are the associated issues for an improved regulatory framework for therapeutics (in particular, to address the calls for incentives and accelerated approval)?
- Does there need to be a better, more formalised, regulatory framework for diagnostics in the UK?
- How can translation to clinical practice be accelerated – what are the issues for clinical infrastructure and training?

Commercialisation and access issues

Sir Michael Rawlins (NICE) provided the NHS view on companion diagnostics and drugs, drawing on the experience of NICE - created to combat inappropriate variation in access to medicines, devices and diagnostics - to ascertain the nature of the evidence required for diagnostic-therapeutic combinations, the valuation of such combinations, and the issues for ensuring uptake by the NHS.

Evidence for clinical effectiveness must be judged in terms of whether it is fit for purpose rather than on how it has been derived (that is, whether from randomised controlled trial, observational study or expert opinion); preferred cost-effectiveness determination is based on cost utility analysis (QALYs). Valuation of the diagnostic-therapeutic combination is calculated in terms of the additional costs and possible benefits, to yield the incremental cost-effectiveness ratio (ICER). Setting a limit on ICER (cost ineffectiveness) can be controversial but is critically important in order to minimise the risk of denying other patients other effective healthcare within the total resource constraints (the opportunity cost). Case study analysis of Trastuzumab combined with evaluation of Her 2 receptor status in breast cancer demonstrated an ICER within the range regarded as cost-effective. Nonetheless, even for this combination of demonstrable value, there are significant issues for ensuring clinical uptake, conditional on the availability of reliable testing procedures, local financial resources for drug acquisition, and the infrastructure for delivery and evaluation (follow up echocardiography).

The conclusions from this case study were that the requirements for clinical evidence are not insuperable, that economic valuation is possible (if the appropriate data have been captured or imputed) and that implementation of NICE guidance requires clinical enthusiasm and resources. Wide-ranging discussion examined the role of NICE and the NHS more

generally with regard to many of the points introduced by previous speakers.

For example:

1. Should the NHS take an active role in searching for drug targeting technologies, in fostering novel clinical methodologies and in collecting new evidence? Sir Michael suggested several areas where an active role was particularly helpful – in oncology, in the replacement of surrogate markers, and in determining comparative efficacy. Reinforcing points made previously, there is a need for better tripartite interaction (between company, Regulatory Authority and NICE) to establish what clinical data should be collected, especially in phase III.
2. What are the opportunities for introducing differential pricing by clinical indication? This is deemed logistically difficult for the NHS.
3. What are the implications of conditional approval – how would NICE handle evaluation if there is less evidence available? It is difficult for NICE to act without some information on patient or health services benefit for a new intervention. However, the principle of piloting rollout with ongoing evaluation of new technology (for example, in cytology) prior to general adoption is well established.

Professor Munir Pirmohamed presented the case study of Cytochrome P450 genetic testing. The Cyp 450 superfamily is involved in the metabolism of many endogenous and exogenous substances such that monitoring activity of Cyp 450 variants might be valuable to individualize drug dose. Cyp 2D6 has been the most widely studied variant, with major impact on pharmaceutical research and development decision-making in certain therapeutic areas, where demonstration of metabolism via Cyp 2D6 may be a deterrent to further development.

However, for those drugs already on the market and known to be metabolised by Cyp 2D6 (for example, many anti-depressants), patient dosing is not yet stratified according to Cyp 2D6 status. The reasons for this lack of impact are various – other Cyp 450 variants may also be involved in fractional clearance, the parent drug may have an active metabolite (for example, nortriptyline and 10-hydroxynortriptyline) such that efficacy may be demonstrated regardless of the rate of metabolism, or there may be confounding factors in the clinical response (for example, high placebo rate, poor patient adherence) obscuring the effect of individual variations in the rate of metabolism.

What further evidence is needed to translate Cyp 450 findings into clinical practice? For warfarin (prescribed to 1% of the UK population and metabolised by Cyp 2C9), genetic variation taken together with age and body weight predicts up to 60% of the variance in maintenance dose. However, the different warfarin dosing algorithms are not transposable between populations and the interpretation of the warfarin research studies to date has been limited by their retrospective nature and exclusion of certain patient groups. The ongoing Warfarin Pharmacogenetics Prospective Cohort Study seeks to collect genotype, clinical information and pharmacological phenotype on 1,000 patients. Interim analysis on one-third of this sample confirms that Cyp 2C9 is important but that the contribution to predicting warfarin dose is much less in the prospective than in the retrospective studies. Additional efforts

to collect the evidence needed to personalise warfarin dosing include a proposed European randomised controlled trial, whole genome association scan to identify new variants and the work of the International Warfarin Pharmacogenetics Consortium to share data to devise a universal dosing algorithm.

Other promising research areas for Cyp 450 pharmacogenetics include the elucidation of polymorphisms in clarifying the lack of response to tamoxifen (Cyp 2D6), characterising codeine toxicity (Cyp 2D6), determining the dose of tacrolimus (Cyp 3A5) and defining the response to proton pump inhibitors (Cyp 2C 19). An instructive pharmacogenetic case study is also provided by the analysis of Abacavir hypersensitivity in association with HLA B57. The UK introduction of pre-prescription B57 genotyping is a good example of improved cost utility impacting on both patients and the manufacturer – a reduced incidence of hypersensitivity and an increased use of Abacavir.

One key issue raised in discussion concerned the standard of evidence required to inform drug labelling. Regulatory Authorities are not consistent on whether label changes can be based on retrospective evidence (that may overemphasise the impact of genetic variation) and the recent action of the FDA to amend the warfarin label is controversial. However, generation of higher quality data through prospective study is expensive – reinforcing the importance of answering the question, ‘who pays?’

Reforms to drug discovery and development

In seeking practical solutions to the many issues raised during the formal presentations and their discussion, two Breakout Groups were convened. Group 1 discussed reforms to drug development, particularly in the context of the recommendations from the Cooksey review and its implications for incentivising stratified medicines. Group 2 was tasked with exploring ways to encourage the rapid uptake of proven therapeutic innovation together with capturing the changing value of stratified medicine products throughout their lifecycle.

Outputs to Group 1 discussion are summarised in Box 2.

Several cross-cutting themes emerged from Group 1 discussion:

Enabling partnership

The paradigm for early drug development might need to change to allow public funders to conduct First in Man studies in order to generate fundamental knowledge on disease heterogeneity, proof of mechanism and biomarkers. Information from compounds that fail may be as useful as the information from those that work. The value of this public support – a logical outcome of the Cooksey review – has implications for OSCHR advice on research and development priorities as well as for industry, which must decide if it is interested in sharing some of the development risk (while protecting company IP and responsibility for research and development decisions). If the UK can create a facilitatory environment for early development, then cooperative mechanisms

Box 2 Reforms to drug discovery and development

Baseline assumptions

- There is no single model of research and development.
- Drug development should be viewed as a continuum, spanning pre-and post-approval.
- There must be focus on clinical utility, not just safety and efficacy.

Public investment in science

- Need to build the underpinning knowledge base and use of biobanks for hypothesis generation and testing.
- Key role for public-private partnerships, but what are the IP implications?

Enabling pre-approval medicines stratification

- Need for flexible phase III trial design based on emerging clinical response and biomarker data.
- Reform of approval requirements – especially when phase III studies are negative in non-stratified populations.
- Need to resolve issues for simultaneous availability of diagnostic and therapeutic.

Enabling post-approval medicines stratification

- Is the only realistic way to stratify for safety?

Need to eliminate disincentives to companies (i.e. introduce value-based pricing).

Cooksey conditional approval

- A specific example of post-approval stratification.
- May permit simultaneous development of diagnostic and therapeutic.
- Enables better stratification for emerging adverse events - if pharmacovigilance is robust.
- Will only apply to high medical needs (e.g. oncology, inflammatory disorders, neurosciences) and requires open dialogue on risks and benefits between payor, regulator and company.

can be expected to accelerate research and development and the reduction of early costs might then allow more to be invested in later surveillance for adverse events.

However, as resources are always limited, might the public funders have to choose between their investments in early or late development? Phase III represents a singular opportunity for the collection of biomarker samples to inform stratified medicine delivery but the costs of sample collection and storage are high and there may be ethical issues in using individual data. Following the Cooksey review recommendation for conditional approval, OSCHR may wish to take the initiative to build public-private partnership in phase III, to answer fundamental science questions, although companies would need to reconcile a more collegial culture in late development with their customary highly-competitive business model. It must also be appreciated that many phase III trials are multinational with only a small UK contribution. Thus, discussions need to be progressed internationally although it is also true that the UK contribution might grow if the UK is perceived as an increasingly attractive location for patient recruitment and the access of patient information. The inception of the UK Clinical Trial Networks is an important initiative in this regard.

What is increasingly clear is that many in both the public and private sectors see scientific value in building collaboration in the research and development pathway and that the UK has potential to capitalise on the analysis of aggregated data sets (from the General Practice Research Database currently and from biobanks and Connecting for Health in the future). Increasing collaboration has the added advantage of inculcating a less confrontational culture for dialogue on drug risk and uncertainty.

Timing of therapeutic-diagnostic development

It is often unrealistic to expect development of a companion diagnostic by the time of

launch of the therapeutic although there may be fortuitous occasions when biomarker data can be generated in phase II in time to inform phase III and this will be more likely when there are public initiatives to invest in the generation of fundamental knowledge, as described previously.

There is a risk of unintended consequences in premature selection of a biomarker if there is only limited understanding of the relationship between biomarker and clinical outcome. Thus there is a need to reform the development process to permit adaptive and flexible trial design to pursue emerging ideas – for example, to capture increasing information on the utility of biomarkers – not necessarily conceived when the company first constructs its clinical trial programme in negotiation with the Regulatory Authority. While the options for co-developing therapeutic and diagnostic will remain challenging, the prime need is to collect the appropriate samples – without these no option is feasible.

Incentives

As already noted, a pharmaceutical company has the incentive during its research and development processes to use stratification strategies to target development and maximise drug uptake but once a drug is launched, further stratification becomes a disincentive to companies (reducing their market size). If this disincentive results in companies withdrawing from research and development then stratification will also operate counter to public goals for the availability of effective medicines. While there may be factors offsetting the disincentive – for example, greater market penetration of the smaller sub-group or rescue of a compound that will fail without stratification – it is an important challenge for public policy-makers to reduce the disincentives for post-approval stratification. The primary obstacle is a fixed price. The Breakout Group concluded that if value-based reimbursement and pricing is possible then pharmaceutical companies are more likely to invest in stratified

medicines, confirming the assumption made at the beginning of the meeting. Therefore, the key element in encouraging companies to volunteer for the Cooksey proposed option of conditional approval is the ability to re-negotiate price once utility is established. Companies are willing to engage further in defining the options for 'making the Cooksey recommendations work' but observe that it is now important to extend discussion to the EU level if clinical partnership and conditional approval are to be adopted more widely.

Fostering uptake of innovation

Related points on incentives emerged from Breakout Group 2 discussion, as part of

a series of suggestions on a value-based socially-constructed system to encompass both therapeutics and diagnostics (Box 3). Group 2 discussion also reinforced previous points about the importance of drawing on a range of clinical utility evidence and the imperative of collecting better evidence now rather than waiting for the impact of Connecting for Health. Building early engagement in new types of public-private partnership (therapeutic and diagnostic companies together with payors) and opportunities at the EU level were confirmed as complementary to the provision of incentives to individual companies in support of the identification and validation of biomarkers to predict safety and efficacy.

Box 3 Fostering uptake of innovation and capturing changing value

Baseline assumption

- It is important to develop a framework to cover both in vivo (molecular imaging) and in vitro diagnostic tests.

Raising the evidence base – the need for new public-private partnership

- Opportunities to use a wide range of study data are now available.
- Need for better post-market surveillance to identify signals more quickly.
- Who generates the evidence on older drugs?

Implementing a value-based not cost-based framework for diagnostics

- NHS silos do not respond well to value arguments because of the difficulty of transferring budgets.
- The goal is value-based pricing for diagnostics as well as therapeutics – what are the additional options for conditional approval of diagnostics?

IP reform for diagnostics

- Multiple competitive challenges (e.g. home brew tests developed by customers).
- What are the options for data exclusivity (non-appropriability)?
- Is IP protection enforceable (if it requires litigation against customers) and does the licensing body have a role in enforcement?

Incentives for pharmaceutical companies to stratify

- Identifying value (QALY-based) is crucial in allowing higher prices.
- If a company does not stratify then it risks the product not being used (adverse events) or imposition of testing by the payor.
- For the future – if the NHS only pays for responders, then the company must target.

Conclusions from the meeting

In summarising the meeting, **Professor John Bell PMedSci** concluded that stratification is desirable for patients, healthcare systems, pharmaceutical and diagnostic companies, and that a compelling socio-economic case can be made. Assuming that scientific advances will create new opportunities for stratified medicines, the obstacles reside in the regulatory, pricing and healthcare systems:

- In the challenge to define stratification prior to drug registration, because of the problems for simultaneous diagnostic-therapeutic development.
- In the weakness of incentives for diagnostic companies, because of the problems for IP protection and cost of demonstrating clinical utility.
- In the weakness of incentives for pharmaceutical companies because the current environment lacks pricing flexibility.
- More generally, because the infrastructure with which to assess clinical utility does not always exist.

Therefore, the key messages emerging from this meeting for policy-makers are:

1. It is essential, for societal as well as pharmaceutical company benefit, to relate therapeutic incentives to pricing flexibility.

Incentives could be linked to value defined after a conditional approval period - the strategic options need to be clarified.

2. For the diagnostic sector, the options for IP protection need further thought coupled with broader consideration of how to reward investment in diagnostics and facilitate companies in their clinical development programmes.
3. Following on from the Cooksey review, there are new opportunities for public-private partnership to establish clinical utility. These opportunities include greater academic involvement in generating fundamental knowledge in exploratory drug development (for example, identifying biomarker signals) and use of public infrastructure for clinical trial sample collection, to inform the conditional approval programme and assist pharmacovigilance. There is also a need to develop a better framework for clinical diagnostic evaluation.
4. There is consensus that the Cooksey review proposal on conditional approval is worth exploring further as a means to become more flexible in assessing stratified medicines.

Related work by the Academy of Medical Sciences

Work by the Academy has addressed other aspects of some of the issues raised in this meeting. The Academy documents that may be found particularly relevant are:

1. Academy of Medical Sciences FORUM (2005). *Safer Medicines*. <http://www.acmedsci.ac.uk/p99puid61.html>
2. Academy of Medical Sciences FORUM (2006). *Experimental medicine symposium*. <http://www.acmedsci.ac.uk/download.php?file=/images/event/EMsum>
3. Academy of Medical Sciences FORUM (2007). *Report of meeting on the Cooksey review and OSCHR strategy*. <http://www.acmedsci.ac.uk/download.php?file=/images/event/FORUM>
4. Academy of Medical Sciences FORUM (2007). *Cooksey Review Response*. <http://www.acmedsci.ac.uk/p100puid112.html>
5. Academy of Medical Sciences (2007). *Careers for Biomedical Scientists and clinicians in Industry*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication>

Annex I: Meeting programme

Sunday 16 September

Reception & Dinner: Meeting overview

Welcome: Professor John Bell PMedSci, President of the Academy of Medical Sciences

Dinner Speaker: Dr Scott Gottlieb, Resident Fellow, American Enterprise Institute

Monday 17 September

Session 1 – Economic issues: creating and rewarding value

Chair: Dr Finley Austin, Head of US External Research & Innovation Environment, Roche

Economics of stratification

Dr Louis Garrison, Professor and Associate Director, Pharmaceutical Outcomes Research & Policy Programme

Case study of value creation and capture: Osteoporosis

Professor Adrian Towse, Director, Office of Health Economics

Session 2 – R&D issues: processes and implications

Chair: Dr Scott Gottlieb, Resident Fellow, American Enterprise Institute

Innovation and drug development: achieving enhanced clinical utility through stratification

Dr Chris Chamberlain, Disease Biology Area Biomarker Expert (Inflammation), Roche Products

Development and integration of molecular imaging in stratified medicine

Dr Jens Sørensen, Medical Director, GE Healthcare

Session 3 – Proposed reforms to enhance innovation and development in the UK

Chair: Professor John Bell PMedSci, President, Academy of Medical Sciences

The Cooksey Review – ABPI perspective

Dr Richard Barker, Director General, ABPI

The problem of pharmaceutical R&D incentives in a single-price market

Dr John E. Calfee, Senior Scholar, American Enterprise Institute

Panel discussion with all speakers

Chair: Professor Munir Pirmohamed, Professor of Clinical Pharmacology, University of Liverpool

Reception & Dinner

Tuesday 18 September

Session 4 – Commercialization and access issues

Chair: Professor Alex Markham FMedSci, Professor of Medicine, University of Leeds

The NHS view on companion diagnostics and drugs

Sir Michael Rawlins FMedSci, Chairman, NICE

Case study: Cyp 450 testing

Professor Munir Pirmohamed, Professor of Clinical Pharmacology, University of Liverpool

Breakout Sessions

Briefing: Dr Finley Austin, Head of US External Research & Innovation Environment, Roche

Group 1 – Reforms to drug development

Moderator: Dr Richard Peck

Rapporteur: Dr Robin Fears

Exploring the likely positive and negative consequences of various drug development reform proposals on incentivizing stratified medicine development. Proposing and exploring alternatives.

Groups 2 – Fostering innovation uptake and capturing changing value

Moderator: Dr Finley Austin

Rapporteur: Professor Adrian Towse

Exploring ways to encourage rapid uptake of proven therapeutic improvements and address capturing the changing value of stratified medicine products throughout the life cycle. Developing proposals for reforms.

Breakout sessions report back**Conclusion – Creating a better world**

Chair: Professor John Bell PMedSci, President, Academy of Medical Sciences

Annex II: Meeting Delegates

Dr Jonathan Allis	GE Healthcare
Dr Finley Austin	Roche
Dr Richard Barker	The Association of the British Pharmaceutical Industry (ABPI)
Professor John Bell PMedSci	Academy of Medical Sciences (AMS)
Dr Ernst Berndt	MIT Sloan School of Management
Dr John E. Calfee	American Enterprise Institute
Mr Richard Carter	Department of Health
Dr Chris Chamberlain	Roche
Dr Deven Chauhan	Office of Health Economics
Dr Alan Davies	GE Healthcare
Professor Sally Davies FMedSci	Department of Health
Dr Robin Fears	Academy of Medical Sciences
Dr Robert Frost	Academy of Medical Sciences
Dr Louis Garrison	University of Washington
Dr Scott Gottlieb	American Enterprise Institute
Dr Adriano Henney	Astrazeneca
Dr Graeme Holland	GE Healthcare
Professor Edward Holmes	Biomedical Research Centre
Dr Orest Hurko	Wyeth Research
Dr Jonathan Knowles	Roche
Mrs Mary Manning	Academy of Medical Sciences
Professor Paul Matthews	GlaxoSmithKline
Professor Alex Markham FMedSci	University of Leeds
Dr Duncan McHale	Pfizer
Dr Greg Page	Roche
Dr Richard Peck	Eli Lilly
Professor Munir Pirmohamed	University of Liverpool
Professor Chris Price	University of Oxford
Sir Michael Rawlins FMedSci	National Institute for Health & Clinical Excellence (NICE)
Dr Severin Schwan	Roche
Dr Jens Sørensen	GE Healthcare
Professor Adrian Towse	Office of Health Economics
Dr Ron Zimmern	Public Health Genetics Unit



Academy of Medical Sciences
10 Carlton House Terrace
London, SW1Y 5AH

Tel: +44(0)20 7969 5288
Fax: +44(0)20 7969 5298

Email: info@acmedsci.ac.uk
Web: www.acmedsci.ac.uk