New Technologies and Biomarkers:
The Way Forward

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CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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WORKSHOP ON NEW TECHNOLOGIES AND BIOMARKERS:
THE WAY AHEAD

SECTION 1: OVERVIEW

The Workshop

Once again, the CMR International Institute for Regulatory Science assembled an impressive team of regulatory, industry and academic speakers to address the topical issue of integrating new technologies, especially biomarkers, into new drug development in a scientific and practical way, within the bounds of economic reality.

In the first Session, chaired by Dr Murray Lumpkin, Deputy Commissioner, FDA, the business case for investing in the development of new technologies and biomarkers was reviewed by the President of Pfizer Global R&D, Dr John L. LaMattina. A panel of speakers, Dr Marisa Papaluca Amati EMEA, Shigeki Tsuda, PMDA and Dr Chris Webster, Millennium Pharmaceuticals, USA, gave regulatory and industry perspectives on the new methodologies for the development and registration of new medicines.

Under the Session heading 'Promises, practices and pitfalls' Dr Johannes Tauscher, Eli Lilly & Co., USA and Prof Klaus Lindpaintner, Roche, Switzerland looked (respectively) at the potential biomarker role of imaging and genomics, whilst Dr Joe Hackett, CDRH, FDA, USA discussed the regulatory implications for the drug-device interface

In the second half of the Session, chaired by Omer Boudreau Director General, TPD, Health Canada, the regulatory framework for validation of biomarkers was discussed by Dr Larry Lesko, FDA, whilst Dr David Jefferys, Vice President, Eisai, looked at the feasibility of harmonisation within and across the ICH regions. Joint research consortia and the integration of the new technologies into development were examined from a legal viewpoint by Gregory Levine, Partner, Arnold & Porter LLP, USA, and from a pharmacoeconomic viewpoint by Professor Louis Garrison, University of Washington.

Syndicate discussions

The Syndicates, that convened in the second half of the meeting were charged with the task of identifying key factors and making recommendations on 'the way forward' to optimise the development and utilisation of new technologies and biomarkers.

Recommendations on consortia

The value of the consortium approach to the development and validation of biomarkers was endorsed by the Workshop. From a company perspective, the motivation for joining consortia is stronger for biomarkers and technologies used in early phase development especially in relation to the natural history of diseases, but it was recognised that the scale of clinical data required for validation of biomarkers in later phases may also be beyond the scope of any single party.

There were concerns that there is little cross-regional or international coordination and it was recommended that ***an international forum should be established to encourage debate between key regulatory and industry experts and biomarker consortia leaders***. It was proposed that The Institute for Regulatory Science could have a role in initiating, or catalysing the formation of such a forum.

Two further recommendations were related to information from, and information about, consortia:

The publication, in the public domain, of information on the work of consortia is essential for increasing information and building confidence among all stakeholders.

There is a need for a directory of information on current and future consortia and the scope of their activities.

Recommendations on validation

The proposals on validation again reflected concerns that different groups and consortia appear to be working in isolation and that the benefits of their work may not be maximised.

It was recommended that pilot studies should be undertaken in one or two therapeutic areas of unmet medical need (e.g., Alzheimer's disease and osteoarthritis) with a view to drawing up 'best practices' for biomarker validation.

It was suggested that a 'Special Focus' workshop, hosted by the Institute might catalyse such studies.

There was also a recommendation on the need for a ***classification (taxonomy) of the different types of biomarker (e.g., imaging, genomic susceptibility, safety and efficacy predictors) in order to categorise and differentiate the criteria for validation***.

Whilst it was emphasised that premature regulatory action should be avoided *it was agreed that* ***the subject should be referred to the International Conference on Harmonisation (ICH) to initiate action at the appropriate stage, although the need for understanding and acceptance of the use of biomarkers extends beyond the geographical regions of ICH***

Other recommendations

The discussions of both consortia and biomarker validation highlighted the large amounts of undisclosed data that are held in the data stores of companies and regulatory agencies, especially in relation to abandoned projects and failed applications.

It was proposed that the Institute for Regulatory Science should include in its future work programme a Workshop to discuss the issues surrounding transparency and data sharing.

The development of Safety Biomarkers was felt to be a neglected area with the current emphasis being on technologies to demonstrate efficacy.

It was recommended that there should be increased efforts to develop and promote the use of biomarkers in resolving safety issues.

There were discussions of the need for additional retrospective analyses of samples obtained during clinical trials as well as possible additional studies to reveal indicators of potential toxicity, once safety issues emerge in the post-authorisation stage. This led to the view that patients need to be convinced to take an 'altruistic' attitude in order to support the recommendation that ***companies should retain tissue samples and imaging data from treated and non-treated patients in clinical trials with consent to carry out retrospective studies.***

Further recommendations related to:

- A future Institute Workshop on the regulatory issues around ***drug-diagnostic combinations*;**
- Possibilities for allowing information on the use of biomarkers ***to be included in labeling*** as an incentive and way of promoting change:
- Examining the ***lessons to be learnt from other successful consortia*** in different technical sectors.

A 'matrix' of recommendations

The wide-ranging debates within the Syndicate groups, ranging from the technical to the philosophical revealed the complexity and diversity of the issues involved.

The main issues, however, were neatly encapsulated in a 5x5 'matrix' that identified five main groups of 'players and five main headings for characterising the factors that are pivotal to moving these topics forward.

- The players: **Industry; Regulators; Patients; Practitioners/payers; Government.**
- The headings: **Policy/politics; Quality; Regulatory; Society; Technology (PQRST).**

Synopsis of the matrix

The following summarises the factors identified as being pivotal to ensuring that biomarkers and the new technologies will lead to optimised therapy.

Industry: Companies should seek active involvement in pre- and 'pro'- competitive consortia and collaborations focusing on the development and validation of biomarkers and there should be a willingness to share databases. The appropriate integration of advanced technologies into drug development is to be encouraged and there is a shared responsibility to reach out to the public in order to demonstrate openness and build trust in new research methodologies.

Regulators: Agencies are responsible for implementing practices that provide incentives for developing new technologies. They need an appropriate IT infrastructure that can be shared with industry as they have unique data resources. Data mining could assist the development of disease models and technical standards. Promoting international harmonisation will have an impact on public confidence in new technologies.

Patients: There is a need for education about the role of biomarkers in medicines research in order to ensure that informed patients can be involved in health-related decisions. Bringing such complex scientific issues 'to the public' in a way that promotes understanding is a priority. Patients have a shared responsibility to facilitate research by becoming part of the 'smart card' information age and by consenting to DNA and other biological samples being retained for retrospective studies, in the interests of advancing science.

Practitioners and payers: Professional bodies should include the role of biomarkers in their continuing education programmes and there should be adequate resources for the on-going education of all parties. Health professionals and payers have a place in discussion of technical standards and should address value-based pricing and reimbursement to reflect the role of new technologies in development. The cooperation of practitioners is essential in achieving the full potential of disease registries and electronic medical record databases.

Government: It should be a priority for governments to provide funding for basic scientific research to support the new technologies. There is also a government role in adopting reimbursement and other health economic policies that do not stifle innovative development and in providing the legal framework to protect the privacy of patients' data in order to foster public confidence.

The establishment of adverse reaction databases and support for effective, linked electronic medical record databanks is also pivotal to future research on the epidemiology and history of diseases and the validation of biomarkers.

[1]The full matrix is reproduced in: Section 2: Summary Report

WORKSHOP ON NEW TECHNOLOGIES AND BIOMARKERS:
THE WAY AHEAD

SECTION 2: SUMMARY REPORT

OUTCOME OF THE SYNDICATE DISCUSSIONS

Session 3 of the Workshop, during which the syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada.*

The Workshop participants formed four Syndicate groups to discuss the issues arising from the Workshop presentations and to make recommendations on the way forward. Topics were discussed under the two general headings of *Collaboration, consensus and confidence-building* and *Ensuring that the new technologies and biomarkers achieve their full potential.*

The Chairpersons and Rapporteurs for the four groups were:

Syndicate 1	*Chair:*	**Dr Ed Harrigan**, *Senior VP, Worldwide Regulatory Affairs and Quality Assurance, Pfizer Inc., USA*
	Rapporteur:	**Dr Paul Huckle**, *Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline, UK*
Syndicate 2	*Chair:*	**Dr Marisa Papaluca-Amati,** *Deputy Head of Sector for Safety and Efficacy, Pre-Authorisation Human Unit, EMEA*
	Rapporteur:	**Dr Graham Burton**, *Senior Vice President, Celgene Corporation, USA*
Syndicate 3	*Chair:*	**Professor Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK*
	Rapporteur:	**Dr Stewart Geary**, *Deputy Director, Eisai Co Ltd, Japan*
Syndicate 4	*Chair:*	**Dr Tim Franson**, *Vice President, Global Regulatory Affairs, Lilly Research Laboratories, USA*
	Rapporteur:	**Professor Bruno Flamion**, *Chairman, EMEA Scientific Advice Working Party, EU*

The programme for the Workshop is set out in *Annex 1* and *Annex 2* gives highlights and extracts from the presentations at the Workshop, especially where these relate to the discussion points and recommendations summarised below.

DRIVERS AND BARRIERS TO BIOMARKER DEVELOPMENT AND USE

The Workshop recommendations were made against a background of more general discussions of the factors that encourage and deter companies when integrating the use of biomarkers into development programmes.

Drivers include:

- Potential for an improved benefit/risk balance and faster market access as a result of using validated efficacy and safety biomarkers;
- Expectations that there will be international support for biomarkers that meet the critical combination of disease burden, available technology and economics;
- Opportunities arising from the increased interest in preventive medicine and potential for biomarkers in this field, although the 'health politics' and attitude of health insurance bodies will vary from one region to another;

- Anticipation that evidence-based biomarkers will be developed, related to the natural course of the disease although there will be reservations about the scale of the epidemiological studies that might be necessary to achieve this.

Barriers include

- The need to overcome the considerable lack of understanding of the role and potential of biomarkers by the public, health professionals and the payers;
- The lack of resources and the reluctance to fund the basic research into disease mechanism that lies at the heart of biomarker development;
- Uncertainty about the feasibility of cross-regional and international agreement on requirements for validation of biomarkers for regulatory purposes;
- Payer pricing and reimbursement systems that do not respond flexibly to changing knowledge of biomarkers in a manner that rewards innovation based on new value-creation
- Requirements for hard end-points, rather than surrogates, before reimbursement will be agreed in some situations, including orphan medicine development;
- The question (noted above) of whether evidence-based validation of biomarkers would be affordable.

Validation hurdles

Three different 'levels' of validation for biomarkers and surrogates were identified, which have an impact on any discussion of criteria and expectations:

- *Level 1 Development/Proof of concept*: Whether company researchers and regulators are satisfied that efficacy and safety decisions can be made at key points in the development and the approval process, on the basis of biomarkers;
- *Level 2 Health outcomes:* Whether those paying for healthcare are satisfied that surrogate endpoints have been validated to the extent that justifies reimbursement;
- *Level 3 Utility in healthcare systems:* Whether society can accept the role of biomarkers in healthcare systems, as a whole.

A MATRIX OF KEY FACTORS

The syndicate discussions highlighted the complex nature of the issues surrounding the validation of biomarkers, the acceptance of surrogate clinical endpoints and the integration of new technologies into new medicines development.

In order to bring some order into the array of views expressed and the recommendations that were made, a 5x5 'matrix' was developed that identified five key 'players':

- **Industry; regulators; patients; practitioners/payers; government**

and five headings (using the acronym PQRST) for the key facilitating factors for ensuring that biomarkers and new technologies will lead to optimised therapy.

- **Policy/politics; quality; regulatory; society; technology.**

This matrix is given on page 9, and the following summary of recommendations and discussion points from the Syndicates describes some of these factors in more detail.

RECOMMENDATIONS

CONSORTIA ON BIOMARKERS

The value of the consortium approach to the development and validation of biomarkers was endorsed by the Workshop

There was extensive discussion of the advantages and drawbacks to being involved in consortia but the balance of opinion recognised that the way forward to study the basic science and make progress on the validation of biomarkers was through joint action that includes industry, regulators and academia.

Discussion points for joining consortia or for acting independently included the following:

- Access to a broader pool of composite data from companies and academic sources helps further scientific knowledge about the aetiology and history of disease.
- For biomarkers in early phase development, that are primarily used for internal company decisions on whether to progress a project, there may be advantages in acting at a local level and not entering into broader coalitions.
- Biomarkers and surrogate endpoints for the assessment of clinical effectiveness at a later stage have broader implications where all parties would benefit from a consortium approach to validation and the adoption of methodologies.
- Consortia increase the available resources for data collection: the scale of clinical work for true validation of a biomarker may be beyond the scope of a single party.

The discussions led to further recommendations related to Consortia.

International discussion forum

There is currently a danger that different consortia are working independently within their own field of interest and with little exchange of views with other bodies also involved with the development and validation of biomarkers. This makes it difficult for other stakeholders to engage across different consortia and is likely to lead to a diversity of approach that will be difficult to overcome when questions of harmonisation arise.

It is recommended that an international forum should be established to encourage debate between key regulatory and industry experts and biomarker consortia leaders.

The Institute for Regulatory Science could initiate the establishment of such a forum which would include the following in its remit:

- Avoiding duplication and building consensus across regions
- Implementing the use of biomarkers and surrogates on a global basis;
- Developing a harmonised approach to the use of these as routine regulatory tools;
- Identifying common experience that could support the development of regulatory guidance;
- Integrating the new technologies into drug development regardless of the region, such that a single global development plan remains viable;
- Ensuring that other stakeholders, particularly health technology assessors and health care providers (payers) are included in the discussions;
- Finding ways to include patient advocacy groups and patient representatives;
- Identifying additional sources of funding and resources.

Sharing knowledge

It was acknowledged that there is currently much activity in terms of workshops and discussion on topics related to biomarkers and it was anticipated that there would be increasing educational efforts through professional bodies, academics curricula and scientific conferences.

The publication, in the public domain, of information on the work of consortia is essential for increasing information and building confidence among all stakeholders.

The example was given of the work being undertaken by the Critical Path Institute and the importance of ensuring that reports are made available in terms that can be understood by the educated public.

Such information should also highlight projects that focus on improving safety and on treatments for unmet medical need. The ways in which all interested parties – patients, physicians and health care providers – can have a 'place at the table' should also be discussed

Inventory of consortia

There is a need for a directory of information on current and future consortia and the scope of their activities.

This may be a major task that should be undertaken by an organisation such as IFPMA that could then make the information available via a portal on their website.

On a more modest scale, an inventory of current activities could be confined to a few key areas (see also the recommendations on Validation, below). This could be a study for a research student, possibly as a scholar under the auspices of The Institute for Regulatory Science[1].

VALIDATION

Whilst every effort should be made to establish generally accepted approaches to biomarker validation, it is also important to avoid premature regulatory guidelines or requirements that could stifle innovation.

It was recommended that pilot studies should be undertaken in one or two therapeutic areas of unmet medical need (e.g., Alzheimer's disease and osteoarthritis) with a view to drawing up 'best practices' for biomarker validation.

Such studies would need to be carried out on a consortia basis, following the principles set out above and would start with an inventory of existing initiatives in these therapeutic fields.

The objectives would include:

- Establishing a broader understanding of the state of science, especially on the progress of disease;
- Pooling information on biomarkers that have been included in regulatory applications as a basis for discussing a harmonised approach to accepting 'known valid' biomarkers;
- Setting out a 'roadmap' approach to biomarker validation;
- Identifying common approaches such as the number and size of studies needed for validation.

There may be a role for the Institute for Regulatory Science in catalysing such studies, perhaps through the organisation of a 'Special Focus' workshop.

[1] The Institute provides facilities and support for MSc ad PhD students whose studies are jointly supervised with the Welsh School of Pharmacy, Cardiff University.

Level of Evidence for Biomarkers

There was discussion of whether there is a 'sliding scale' of evidence that is required for the acceptance of biomarkers used at different stages in the development programme, for example whether a lower level of evidence is acceptable for Phase I and II biomarkers compared with requirements for biomarkers to demonstrate efficacy in Phase III and obtain registration.

There was consensus that a high level of evidence was required at the later stages but views were divided on the use of biomarkers in the earlier stages:

- If the highest standards are applied to all biomarkers this could act as a deterrent to the development of new ones;
- Decisions on, for example, proof of concept or dose selection, have major implications for the future of the project and research investment and it would be hard to justify applying a lower standard of evidence, at that stage.

Taxonomy of biomarkers

There is a need for agreement on a classification of the different types of biomarker (e.g., imaging, genomic susceptibility, safety and efficacy predictors) in order to categorise and differentiate the criteria for validation.

Different types of biomarkers need to be discussed differently in terms of data requirements as noted in the discussion of levels of evidence above. This needs to be addressed before the stage of developing and harmonising regulatory guidance is reached.

Role of ICH

At a certain stage, handling biomarker validation issues on a case-by-case basis will need to be replaced by more specific regulatory guidance and, similarly, agreement on 'best practices' will need to be formalised.

It was agreed that the subject should be referred to the International Conference on Harmonisation (ICH) to initiate action at the appropriate stage, although the need for understanding and acceptance of the use of biomarkers extends beyond the geographical regions of ICH.

SHARING DATA

Biomarker validation requires large amounts of data, collected over a long period of time and covering a variety of products. Consortia on the development and validation of biomarkers can only function effectively if there is a willingness on the part of industry and regulators, to enter into agreements to disclose and share data.

It was proposed that the Institute for Regulatory Science should include in its future work programme a Workshop to discuss the issues surrounding transparency and data sharing.

Data requirements for biomarkers would be a major, but not the only, theme of such a workshop, which would have a wider remit to cover the whole question of the vast amounts of data on failed compounds and projects that could hold valuable lessons for future research and reduce redundancy and duplication of effort.

Discussion points

- It is easier to share data on safety where the issues relate to many different products. The example of QTc prolongation was raised in this context.
- The evolution of electronic submissions means that regulatory agencies have an invaluable store of electronic data and there is an onus on them to facilitate access to that data:
  - It was recognised that there are scientific, legal and ethical issues to be addressed;

  - There are also major funding and resource implications: Who pays? Who would evaluate the data? Who could have access?
- Invaluable data also lies in the company records of products that fail, particularly during Phase III;
  - There are similar questions of resources and confidentiality to be addressed if such information is to be released;
  - It must be recognised that data on failed compounds will be incomplete and may be of little value as companies would not normally commit resources to following-up reasons for failure.
- The potential value of data from electronic databases of medical records should also be discussed at a workshop on transparency. The UK General Practice Research Database (GPRD) was cited as an example.

SAFETY BIOMARKERS

It was recommended that there should be increased efforts to develop and promote the use of biomarkers in resolving safety issues.

With the ever-increasing emphasis on safety questions and the prevailing application of the 'precautionary principle' there should be renewed efforts to identify biomarkers that predict, for example, potential hepatotoxicity or nephrotoxicity.

Two approaches were discussed:

- **Proactive:** Basic research to understand the pathogenesis and seek biomarkers for susceptible individuals (consortium approach) as well as development work on individual products;
- **Reactive:** Retrospective studies of emerging safety problems in clinical use. This would be appropriate for collaborative initiatives to collate data from different companies in order to understand better a safety issue across a class of products.

Discussion points

- There is currently a dearth of good safety biomarkers and, possibly, a poor understanding of their proper use (e.g., liver function tests);
- Since safety issues for which biomarkers are sought may apply across a range of products (e.g., QT prolongation) there is an onus on both companies and regulatory agencies to share information and bring it into the public domain;
- Safety biomarkers may, scientifically, be more difficult to develop than efficacy biomarkers:
  - Understanding of the molecular basis of safety is often lower;
  - Lower frequency of occurrence makes study more difficult;
  - Animal models for efficacy are defined by the use of the parent molecule while safety models can be unclear, clouded by high doses and different dose-response relationships
- There are critical liability issues that need to be addressed in discussing safety biomarkers as these could overshadow any public debate on sharing information.

A shared responsibility with patients

Proposals for retrospective studies gave rise to a further recommendation:

Companies should retain tissue samples and imaging data from treated and non-treated patients in clinical trials with permission to carry out retrospective studies.

Such samples would be used to investigate problems that arise during the lifetime of the product but would require the cooperation of trial subjects in providing consent. This would be part of the educational effort to inform patients not only about the use of biomarkers to support individual treatment but also about their potential to improve safety testing for the broader patient population.

DRUG – DIAGNOSTIC COMBINATIONS

It was recommended that a future Workshop organised by the Institute for Regulatory Science should focus on the regulatory issues that arise when the recommended clinical use of a new product involves the mandatory use of a diagnostic.

This could be part of a workshop to discuss the wider aspects of regulating advanced therapies. Situations to be addressed include:

- Cases where a product and a stand-alone diagnostic are approved and marketed separately:
  - The diagnostic is applicable to the use of other medicines.
- Cases where a specific test is developed for use in a clinical programme:
  - Linkage of the drug and diagnostic at approval;
  - The different implications of approval as separate products or as a combined product/test package
- Harmonisation issues where both ICH medicines guidelines and Global Harmonisation Task Force (GHTF) device guidelines are applicable

OTHER DISCUSSION POINTS

Biomarkers and the label/product information

Regulators should consider allowing information on the use of biomarkers to be included in the product label, as an incentive and way of promoting change.

It was suggested that companies might be interested in including information in the product label that biomarker evidence was used to develop the product, in accordance with established scientific and regulatory standards. By allowing a distinction, in the marketplace this could provide a competitive advantage and add to the incentives to research biomarkers.

This would, however, come with obligations, for example:

- Post-marketing surveillance or other studies to confirm the biomarkers;
- Incorporation in risk-management plans.

This would not obligate competitors to use biomarkers that were not completely validated in their development programmes, but they could only include such biomarker results in their approved product label if they were also willing to accept the post-authorisation obligations, as indicated above.

Learning from the past

Useful lessons could be learned from successful consortia, from all disciplines, and these should be studied in relation to optimising the benefits of biomarker collaborations.

Examples outside the medical field include collaboration on international standards in the semiconductor industry and the music industries (technology for downloading music files from the Internet). Within pharmaceuticals, the problem of replacing CFC propellants in inhalation aerosols was addressed by a multi-company consortium. The critical success factors for such undertakings should be examined.

Public confidence in the concept of private-public partnerships and consortia could be increased by referring to these and other similar examples.

Notes on the Matrix

The Matrix of key factors, described on page 2 is reproduced on page 9, opposite.

The 'PQRST' concept was inspired by Dr Tim Franson, Eli Lilly and the tabulation is based on the report of the Syndicate discussion presented by Professor Bruno Flamion.

With regard to priorities, it was proposed that the factors to be addressed in the short-term are those highlighted in yellow. Medium-term priority is given to the areas shaded pink, where the emphasis is on involving patients, physicians, payers and government in decisions to recognise the value of biomarkers and new technological developments. The need to support basic research is also regarded as a priority.

MATRIX OF FACTORS TO ENSURE THAT BIOMARKERS AND NEW TECHNOLOGIES WILL LEAD TO OPTIMISED THERAPY

		1. Industry	2. Regulators	3. Patients	4. Practitioners and payers	5. Government
P	**Policy/ politics**	Consortia and collaboration: Involvement in pre- and 'pro'-competitive initiatives, such as consortia on biomarker development and validation	Incentives and exclusivity: Government may set the policy for encouraging industry to develop biomarkers, but regulators need to implement the structure that is agreed.	Education: The general lack of understanding of the increasing importance of biomarkers should be addressed	Education: Policies are already in place for continuing medical and pharmaceutical education (CME, CPE) and these should encompass biomarkers.	Funds for basic research: It is important that non-commercial research into the science of biomarkers and aetiology of disease is adequately funded.
Q	**Quality**	Validation: Development of consortia that ensure the quality development and validation of quality biomarkers, e.g., predictive toxicology	IT infrastructure: Appropriate information technology is central to reaching the required development quality and this needs to be shared between regulators and industry	Health-related decisions: Mechanism should be sought for patients' to be actively involved in key decisions.	Value-based pricing: The economics of integrating new technologies into drug development must be understood to ensure adequate reimbursement	Health economics: Agencies (e.g., CMS and NICE) have a role in the acceptance of biomarkers through adopting realistic policies on economics.
R	**Regulatory**	Shared databases: Companies should be ready to share databases with regulatory agencies as well as with other companies	Databases and guidance: Regulatory agencies possess part of the databases relevant to biomarker use and are also responsible for the development of any formal guidelines.	Shared responsibly: Patients need to be involved in ways that benefit others, for example retention of DNA samples for retrospective analysis of adverse events	Disease registries: Smaller patient populations in trials increase the need for disease registries, which require patients' agreement and practitioners' cooperation.	Privacy protection: This is pivotal to the integrity of databases of patient records in order to ensure cooperation and compliance by the public.
S	**Society**	Building trust: Reaching out to the public (a joint responsibility with regulators) and avoiding perceptions of 'disease mongering' in order to create or boost sales...	Building trust: Promoting international harmonisation that takes account .of views from different regions of the world is part of the regulatory remit.	Science for the people: Society needs to find ways to make education on technical subjects more readily available – e.g., on the lines of an 'Epcott Centre' for biomarkers.	Education resources: Society needs to ensure that educational opportunities are provided to keep practitioners abreast of new technological developments.	Adverse events banks: These are key to monitoring future development but international cooperation and possible reform of liability laws (tort) need addressing.
T	**Technology**	Appropriate use of biomarkers: Ad hoc assays, validated methodology, adequate trial designs and using multiple biomarkers, when needed	Technical standards: Use of data mining to develop disease models and agreeing technological standards, e.g. a 'taxonomy' for biomarkers.	'Smart card' approach: Patients need to become part of the evolution in technology with information logged electronically and points of contacts provided for their information and education.	Data standards: Health professionals and health providers must be involved in discussions of standards for biomarkers and new technologies.	E-medical records: Developing the IT infrastructure for data banks on tissue samples and medical records that can be shared across regions and disciplines is essential.

ANNEX 1

WORKSHOP PROGRAMME

SESSION 1: THE CURRENT ENVIRONMENT, OPPORTUNITIES AND INITIATIVES	
Chairman	**Dr Murray Lumpkin**, *Deputy Commissioner, International and Special Programs, US Food and Drug Administration*
The business case for investing in new technologies and biomarkers	**Dr John L. LaMattina**, *President, Pfizer Global R&D, USA*
Regulatory acceptance of new technologies and biomarkers in development and registration of new medicines: Ensuring opportunities are seized	
A View from Europe	**Dr Marisa Papaluca Amati** *Deputy Head of Sector for Safety and Efficacy, Pre-Authorisation Human Unit, EMEA*
A View from the USA	**Dr Chris Webster** *Director, Regulatory Strategy and Intelligence, Millennium Pharmaceuticals Inc, USA*
New Technologies and the Review Process in Japan	**Shigeki Tsuda**, *Director of the Office of International Affairs and Human Training of PMDA, Japan*
SESSION 2: PROMISES, PRACTICES AND PITFALLS	
Imaging biomarkers in drug development	**Dr Johannes Tauscher,** *Medical Advisor, Eli Lilly & Co., USA*
Genomics, diagnostics and the promise of 'personalised' medicines	**Prof Klaus Lindpaintner** *Head of the Molecular Genetics Institute, Hoffmann La-Roche, Switzerland*
Regulatory implications for the drug-device interface	**Dr Joe Hackett** Associate Director, Office of *in vitro* diagnostic device evaluation and safety (OIVD), CDRH, FDA, USA
SESSION 2 continued	
Chairman	**Omer Boudreau**, Director General, Therapeutic Products Directorate, Health Canada
Looking backwards to create a sound regulatory framework for the future	**Dr Larry Lesko**, Director, Office of Clinical Pharmacology and BioPharmaceutics, CDER, FDA, USA
Validation of biomarkers: Is harmonisation feasible?	**Dr David Jefferys**, Vice President, Global Regulatory Affairs, Eisai Co Ltd, UK
Use of biomarkers in product development, risk management and product liability defence	**Gregory Levine**, *Partner, Arnold & Porter LLP, USA*
Achieving the potential of the new technologies and biomarkers: A Pharmacoeconomic viewpoint	**Prof. Louis Garrison**, *Professor of Pharmacy, University of Washington, USA*
SESSION 3: SYNDICATE DISCUSSIONS - BUILDING CONSENSUS, CREDIBILITY AND CONFIDENCE	
Chairman	**Professor Robert Peterson**, *Professor of Paediatrics, University of British Columbia, Canada*

SECTION 3

EXTRACTS FROM THE WORKSHOP PRESENTATIONS

The following provides some extracts and 'snapshots' from the information and views provided by the speakers the Workshop. This is not intended to provide a comprehensive or sequential report of the presentations but rather to give the background to the Syndicate discussions and, in particular, to highlight points that were later summarised in the 'Matrix of factors to ensure that biomarkers and new technologies will lead to optimised therapy' (page 9).

The extracts are attributed to Workshop speakers. Please see the programme on page 11 for the full designations of the individuals and the titles of their presentations.

CONTENTS

CONTENTS

1. SCENE SETTING

Biomarkers

1.1 BIOMARKERS

1.1.1 Background

Biomarkers are seen as the answer to increasing the efficiency and speed of pharmaceutical development as well as reducing the costs through:

- Screening potential compounds
- Accelerating proof of concept
- Predictive toxicology and safety differentiation
- Validation of surrogate end points

Two questions to be addressed are whether this optimism is justified and whether it is reasonable to expect this within a timeframe of the next 10 years.

It is important not to overlook the large range of different types of products and techniques that can be classified as biomarkers:

- In vitro diagnostics (from genetic probes to simple biochemical assays);
- In vivo diagnostics
- Imaging techniques, both fixed and dynamic
- Physical measurements

In the current situation, oncology is the most advanced field. In other areas, however, biomarkers are being explored for proof of concept and to identify responders in the design of enrichment trials. At later stages biomarkers have a role in surrogate validation and, in the clinical setting, for monitoring therapy.

Some of these biomarkers are currently regulated under either pharmaceutical or medical device regulations whilst others, particularly those used early in the development process, may not come under specific regulatory control.

Dr David Jefferys

1.1.2 Biomarkers are not new

There are well-established biomarkers and surrogate end points that are known and accepted by health professionals and the public, albeit not under this terminology:

- Blood pressure for cardiovascular disease;
- LDL-cholesterol as a predictor for stroke and myocardial infarction;
- Haemoglobin A1c as a marker for diabetes is not so well known but is now accepted;
- In the viral field CD4 and viral copy number are important in HIV infection.

The existence of valid surrogates such as these reduces the cost of screening drugs for use in humans and help developers to know where they stand before going into an expensive Phase 3 programme.

These types of well-founded, well-established, well recognised biomarkers are, however, rare and this is an area we need to work upon as a driver for major improvements in public health.

Oncology is an area where there has been a very positive increase in the use of biomarkers, especially imaging techniques such as Dynamic Contrast Enhanced (DCE) MRI, and research started in the past few decades is starting to come to fruition, There are, however, slow, degenerative chronic diseases such as osteoarthritis, Parkinson's disease and Alzheimer's where much work is needed in order to identify valid biomarkers.

Dr John L LaMattina

Acceptance of surrogate endpoints has taken time

Some of the major advances have been products from the pharmaceutical industry that were taken forward on the basis of surrogates. These range from blood pressure and cholesterol lowering and glycaemic control through to drug development for HIV/AIDS. A pragmatic approach has been taken and has served the purpose well but the process has not been rapid. For example, it took some 20 years to progress from the approval of labels for cholesterol lowering to the official acceptance of claims for reduced morbidity and mortality. Furthermore it was not until the mid-90s that it was accepted that good blood glucose control leads to reduced complications from diabetes.

Dr David Jefferys

Consortia

1.2 CONSORTIA

1.2.1 US consortia

One of the main drivers towards pre-competitive consortia is that the expense of clinical validation of biomarkers might exceed the economic return for any one company. Another is the need to achieve acceptance, by the regulatory and scientific communities, of new surrogate endpoints. This is, however, not a trivial undertaking and must be carried out in a way that does not violate anti-trust laws.

Examples of consortia in the US

NIH Osteoarthritis (OA) Initiative study

Objectives

- To characterise the natural history of OA in patients with the condition and in subjects at risk of developing OA;
- To characterise and validate outcome and prognosis biomarkers;
- To characterise risk factors for OA progression;

The consortium is a partnership between the US National Institutes of Health (NIH), and four pharmaceutical companies: GSK, Merck, Novartis and Pfizer. It is coordinating a 4-center four-year longitudinal study in 5,000 subjects:

Enrolment started in 2004 and the first public data release is scheduled for 2006.

PhRMA-FNIH-NIH-FDA Biomarker consortium

At the time of the workshop, the launch of this consortium was imminent but had yet to take place and the information that could be released was limited.

It is a private-public partnership formed by the US research-based industry association PhRMA, the NIH, the Foundation of the NIH (FNIH) and FDA.

Membership in the consortium is expected to include a cross-section of pharmaceutical and biotechnology companies, government-funded research institutes, academia and patient advocacy groups

FDA/Critical Path Institute Predictive Safety Testing Consortium

This is a public/private partnership between FDA and a number of pharma companies that is administered by the Critical Path Institute (a non-profit organisation based at the University of Arizona)

The objective is to advance the validation of safety biomarkers with a focus on:

- Kidney injury
- Liver injury, including signals for idiosyncratic reactions
- Vascular Injury
- Carcinogenicity studies

FDA will have substantial involvement and input in all scientific aspects of the Consortium

Alzheimer's Disease Neuroimaging Initiative

This is, again, a private/public consortium, the partners of which are the National Institute on Aging (NIA), the NIH foundation, eleven companies (Pfizer, Wyeth, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Merck, AstraZeneca, Novartis, Eisai, Elan and Forest) the Institute for the Study of Aging, Alzheimer's Association and FDA. The estimated study cost is US$60M

The objectives are to validate candidate diagnostic and disease progression biomarkers of Alzheimer's disease (AD) in a 3-year longitudinal natural history study examining AD, mild cognitive impairment, and aged-matched controls.

The project was funded in October 2004 and recruitment was initiated in September 2005. The last subject visit and the reports are scheduled for 2010.

Dr John LaMattina

The 'PPP' is not the only approach

A preoccupation with 'Private Public Partnerships' must not overlook the value of other types of study and methodologies. The example of the ***Framingham Heart Study,*** based on epidemiological data, and the value of the data to be obtained from linked electronic medical records must not be overlooked as a basis for longitudinal studies. Such methodologies are not necessarily in the design of current PPPs.

Professor Robert Peterson

1.2.2 Involving other stakeholders

Other stakeholders

Do those working in the practice community regard tests that industry treat as 'biomarkers' in the same way or are they unaware that routine disease management tools are, in fact surrogates? Their views need to be taken into account in the on-going deliberations.

This was raised in the discussion sessions and, similarly, it was suggested that both practitioners and payers need to be brought into discussions of the role of genomic biomarkers and the related advice that is given in labelling, with regard to screening patients before a product is administered. There need to be discussion of the criteria for saying that testing should be mandatory, but there are practical and ethical aspects to be addressed. If pharmacogenomic characteristics indicate that some patients are more likely to benefit, does this necessarily preclude others that might derive some benefit?

It is clear that a mechanism needs to be found whereby all interested parties can be included in the discussions and the *Personalised Medicine Coalition* formed in Washington D.C., October 2004 was cited as an example of a consortium that seeks to include a wide spectrum of interests.

Is there a fundamental issue between promoting personalised medicine and the position of officials on public health in general and on affordability in particular? We keep saying personalised medicine will be more cost effective but it will also cost a lot more.

Presentation by Prof. Klaus Lindpainter

It was also pointed out that the validation/qualification of biomarkers is not necessarily carried out for a single purpose, depending upon the stage of development and the purpose for which the biomarker, or surrogate end point is used. During development, biomarkers may only impact internal company decisions on whether to proceed to Phase 2 or may be subject of joint company/regulatory discussions at the end of Phase 2. At the application stage, regulators must assess the use of biomarkers and surrogates in terms of granting a full or conditional authorisation but there are wider implications for health care providers in deciding on payment decisions and for physicians in terms of prescription choices.

The cost of validation, in terms of added value and the impact on treatment outcomes are not necessarily routinely addressed in the development and regulatory process and this is yet another reason for ensuring the participation of a wider range of stakeholders.

From discussion sessions during the presentations

1.2.3 Some 'legal' perspectives

In order to move forward and achieve the potential of biomarkers there will need to be sharing of information with many companies willing to work openly with academia and regulators to pool their data. This can lead to the so-called 'collective action problem', that is, whether a single company has an incentive to collaborate and whether it is in their interests.

This is a legal issue: When you have a collective action problem the solution is often some form of government intervention, although not necessarily legislative. In the USA the government, through FDA, is taking steps to encourage through, for example Voluntary Genomic Data Submission (VGDS) guidance and other initiatives, notably the Critical Path initiative under which companies are encouraged to become engaged in joint research and development projects.

Gregory Levine

1.3 RESEARCH CHALLENGES

Increasing awareness

1.3.1 Awareness of patients, practitioners and payers

The industry objective is to develop medicines that are safe and effective across populations but the general public does not necessarily appreciate the difficulties. Whilst the community readily accepts that some individuals may be allergic to nuts and others are lactose intolerant, there is an expectation that all medicines will work the same way and be safe in all patients whether old or young, male or female and of different genetic populations. The public has unrealistic expectations and this is a hurdle must accepted by companies.

There is also a general lack of understanding of the high attrition rates in the development of medicines and the fact that it takes it takes over 100 discovery approaches to yield a single product. In the mind of the public it may appear that industry 'is not very good at the job'. There is also ignorance of the 12 to 15-year timeline needed to develop a new medicine and the costly nature - over $800 million investment being needed for each marketed product.

Historically we fail 96% of the time. We are trying to double productivity so that we only fail 92% of the time.

The next hurdle facing the developer, that is becoming ever higher, is the increasing role being played by the payer. Developers strive to discover medicines that are an improvement on those already in the market, but you can now have a product that is significantly better than others which, nonetheless, may not be considered a sufficient improvement to be included in a formulary. This presents, for industry, a whole new way of looking at matters.

Dr John L LaMattina

Growing Role of Health Technology Assessment

Globally, payers are requiring more information on the economic impact of new technologies prior to coverage and reimbursement. Companies are gathering and preparing more evidence, although this is currently more common for drugs than for diagnostic tests. Increasingly, however, payers are asking for similar evidence of real-world clinical utility data for new diagnostics.

Dr Lou Garrison

2. GOVERNMENT AND REGULATORY POLICY

2.1 POLITICAL WILL

Political will

2.1.1 Ensuring opportunities are seized in the EU

The EU political context: It is recognised that the pharmaceutical and health care industries are the cornerstone for EU industrial competitiveness and for attaining public health objectives

The EU legal tools:

- Review 2001 of the pharmaceutical legislation, fully implemented, November 2005;
- Draft Paediatric Medicines' legislation to facilitate the development of medicines for children is at an advanced stage of adoption by the European Council;
- Draft Regulation on Advanced therapy medicinal products that will regulate human tissue engineering products, gene therapy products and somatic cell therapy products;
- Draft proposals to amend the Medical Devices Directive 93/42/EEC

The EMEA Road Map to 2010: Preparing the ground for the future, March 2005 provides a long term commitment in support of innovation, in liaison with all relevant stakeholders. All the target dates set out in the Road Map have been met, so far.

The new EU research framework: Innomed (2007-2013). This sets out priorities and opportunities in key areas, including:

- Improved predictability of early safety testing;
- Biomarkers predictive of response in cancer, diabetes, inflammatory diseases, brain diseases, bacterial resistance;
- Data sharing and knowledge management;
- Risk management methodology.

Dr Marisa Papaluca Amati

2.1.2 FDA Critical Path

The motivation for the FDA Critical Path Initiative (see figure 1) was to try to improve productivity. The target of modernising drug development by 2010 is ambitious and there remains a conundrum on biomarker predictive performance: *Why have biomarkers not been more successful in bridging early and late clinical development?*

Biomarkers and surrogates are, however, a focal point of the Critical Path Opportunities List issued in March 2006, which includes the quote: 'Adoption of a new biomarker or surrogate endpoint for effectiveness standards can drive rapid clinical development'.

Figure 1

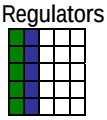
http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Dr Larry Lesko

The nature of regulators
We are not pure scientists and we are not business people. Regulators have a specific responsibility to ensure promotion and protection of public health. We act upon both science and rules. To endorse a new development in pharmaceutical science we need to work with a number of different ingredients.

Dr Marias Papaluca Amati

Industry & Regulators



2.1.3 New technologies and biomarkers: Industry and FDA working together

The current state of collaboration between FDA and industry on new technologies and biomarkers is very strong and can be traced through the chronology of activities from 1999 to the present (Table 1).

Table 1	
1999	NIH Biomarker Symposium
2000	Start of informal educational meetings – Small groups discussing, for example, aspects of microarrays and pharmacogenomics
2002	First major workshop on Pharmacogenomics (PGx) – The concept of voluntary genomic data submissions (VGDS) was proposed: Industry might be able to submit early exploratory data that would not be used for regulatory decision making
2003	**January** – FDA Innovation Initiative (Commissioner Mark McClellan) **March** – PhRMA response with the formation of a Pharmaceutical Innovation Steering Committee (PISC) **November** – Draft Guidance on PGx Data Submissions encapsulating the idea of voluntary submissions and including the new language of probable valid and known valid biomarkers that has been applied to other forms of biomarkers **November** – Second major workshop on Pharmacogenomics
2004	**March** – Launch of the Critical Path Initiative **July** – Third major workshop on Pharmacogenomics – Addressed the co-development of PGx drugs and diagnostics
2005	**March** – Final Guidance on PGx Data Submissions **April** – Draft Concept Paper on Co-Development of PGx Drugs and Diagnostics **April** – Fourth major workshop on Pharmacogenomics **September** – Workshop on qualification of genomic biomarkers – Reports that 20 VGDS submissions had been received by FDA **November** – Major workshop on Proof of Concept **November** – Informal discussion group on pharmacogenomics in ICH under the reference E15
2006	**March** – Critical Path Opportunities List published **April/May** – anticipated launch of the FNIH/FDA/Industry consortium for biomarker qualification

Dr Christopher Webster

There are many possible opportunities for biomarkers in the FDA Critical Path Initiative that have the potential to make development more efficient and predictable. FDA is also becoming very much more open to discussion at a scientific level with opportunities to interact offered under the exploratory IND guidance, voluntary genomic data submissions (VGDSs) and end of Phase 2A meetings. Discussions of model-based drug development and efficient clinical trial designs give opportunities for unprecedented flexibility in innovation.

There are likely to be many other approaches and critical path opportunities to improve productivity. Industry should *focus* and take full advantage of them.

Dr Joe Hackett

2.1.4 New technologies and biomarkers: EMEA initiatives

Innovation

- Establishment of the EMEA Innovation Task Force (2001) to facilitate early contacts with Sponsors (a 'soft landing zone') to identify emerging science and technologies with a potential regulatory impact and to discuss, informally, bottlenecks and opportunities offered in the system
- Development of a new pathway for informal meetings to facilitate the exchange of information at various stages of development and new voluntary processes to complement and reinforce existing procedures
- Establishment of specialised working parties to discuss the impact of emerging approaches on existing regulatory principles and to provide scientific feed back to the sponsors and within the EU network
  - Examples: Gene therapy working party, Pharmacogenomics working party
- Convening workshops with stakeholders to discuss emerging issues and opportunities
  - Examples: Pharmacogenomics Workshop in 2000, Biomarkers workshops in December 2005 and 2006
- Promotion of training opportunities in the EU network
- Establishment of the EMEA Innovation Think-Tank (2004):
  - To support the EC in Innomed/Strategic Research Agenda (SRA) implementation
  - To form a view on current and future scientific development of medicinal products and related regulatory standards in Europe
  - To encourage discussion on innovation and research on pharmaceuticals
  - Identify what is needed in term of science for regulatory purposes

Dr Marisa Papaluca-Amati

2.1.5 Japan: Development of a guideline on pharmacogenomics

Regulatory initiatives

MHLW Notification No. 318001, 18 March 2005, on the Provision of Information to Regulatory Authorities on Development of Guideline on Use of Pharmacogenomics (PGx) in Clinical Studies of Drugs

The purpose was to collect information from companies on their use of PGx in order to develop a Guideline

Information requested:

1. List of clinical studies that were conducted or are being conducted, making use of genomic information (Domestic/foreign trial, race of subjects, disease, target gene, test methods, purpose, tissue banking etc.);
2. List of planned clinical studies;
3. List of finished studies in which post-analysis was conducted (those where banking of samples was established);
4. Whether, for the studies reported under 1-3, results from genomic analyses are to be used to determine the indications, dosage and administration and/or precautions and warnings:
   - Information to include whether there are new analytical methods, diagnostics and/or medical devices being developed concurrently;
5. Information on both pre-approval and post-approval studies;
6. Whether the consent obtained from trial subjects included disclosure of information to regulatory agencies

To take forward global development we need to seize opportunities for joint scientific advice. EMEA and FDA are piloting a scheme under the confidentiality agreement but there is a need to bring PMDA in.

Dr David Jefferys

Collection and use of the information

The time limit for submission of information was 30 September 2005, although companies were asked to submit data as soon as possible. In discussing the guideline, details of the information that had been received were not disclosed because of intellectual property considerations related to the development of new drugs. Disclosure to external experts could, however, be agreed in consultation with the provider.

PMDA was able to ask for further details, based on the information collected by MHLW, but this information was not to be used for the purpose of developing the guideline and not in the approval process or for other administrative purposes.

By the end of September 2005, information had been provided by 21 companies on 179 clinical trial procedures. In addition an analysis of published data is being carried out and an Expert Committee has been formed to develop the guideline. It is expected to take more than two years to finalise the guidance.

Shigeki Tsuda

Regulatory initiatives

2.1.5 Regulatory initiatives in the US

The regulatory pathways that support or facilitate translational drug development perhaps originate with the Food and Drug Modernization Act (FDAMA) in 1997 which, under §115, allows approval of a drug to be based on data from one pivotal study plus "*confirmatory evidence*". This could be interpreted as early acceptance of the biomarker concept. Other regulatory initiatives include the following:

The **Voluntary Genomic Data Submission** (VGDS) guidance allows relatively informal discussion of exploratory genomic data between FDA and companies without risk of its use in decision-making. It is anticipated that similar provisions may be made for voluntary imaging data submission ('VIDS'), including guidance on the standards for submitting imaging data.

Exploratory INDs: This introduces the concept of allowing microdose studies of new drugs with a reduced data burden. The guidance reiterates the key principle of development flexibility and it is envisaged that this could be used for Phase 0 biomarker studies

End of Phase 2a meetings allow early discussion of dose-finding and biomarker data that might help towards reducing attrition rates.

Guidances on technology validation; This provides examples of joint working with industry, in particular the recent guidance on pharmacogenomic and genetic tests. This built on an earlier guidance form 2000 and showed clearly that the revisions had taken account of industry comment and input.

Dr Christopher Webster

Technical issues

3. TECHNICAL ISSUES

3.1 DEFINITIONS AND CHARACTERISTICS

3.1.1 Biomarkers: Finding a definition

A biomarker has been defined as a characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacological response to a therapeutic intervention[1].

This, however, tends to 'silo' biomarkers according to different processes whilst the power of biomarkers that is now emerging from work with disease models is that biomarkers from several domains will be integrated differently to improve predictions of clinical outcome: Physical evidence (imaging), genomic subsets of disease (receptor polymorphism), dose-exposure drivers (metabolism genotypes), exposure-response causal biomarkers (conc/IC_{50} as used for HIV/AIDS)

[1] NIH Definitions Group. Biomarkers and Surrogate Endpoints in Clinical Research. In Downing GJ (ed.) Biomarkers and Surrogate Endpoints. Amsterdam: Elsevier, 2000.
1-9. Clin Pharmacol Ther 2001, 69, 89-95., http://www.fda.gov/cder/genomics/GDS.htm

Put together in a causal chain from giving the drug to looking at a patient outcome they become, collectively, very predictive and this is the direction in which progress is most likely to be made.

Exploratory, probable, known

A new definition of biomarkers has been included in the FDA *Guidance for Industry on Pharmacogenomic Data Submissions* (Table 2) which introduces the concept of *exploratory*, *probable* and *known* valid biomarkers depending on the source and availability of scientific evidence.

Table 2: Extracts from FDA Guidance for Industry on Pharmacogenomic Data Submissions, March 2005

Section III. SUBMISSION POLICY

A. General Principles ……..

This guidance also makes a distinction between pharmacogenomic tests that may be considered either **probable** or **known** valid biomarkers, which may be appropriate for regulatory decision making, and other less well-developed tests that are either observational or **exploratory** biomarkers that, alone, are insufficient for making regulatory decisions. ……

This guidance makes an additional distinction between **known valid** biomarkers that have been accepted in the broad scientific community and **probable valid** biomarkers that appear to have predictive value for clinical outcomes, but may not yet be widely accepted or independently verified by other investigators or institutions (see Glossary). [*Emphasis added]* …….

GLOSSARY

Valid biomarker: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. The classification of biomarkers is context specific. Likewise, validation of a biomarker is context-specific and the criteria for validation will vary with the intended use of the biomarker. The clinical utility (e.g., predict toxicity, effectiveness or dosing) and use of epidemiology/population data (e.g., strength of genotype-phenotype associations) are examples of approaches that can be used to determine the specific context and the necessary criteria for validation.

- **Known valid biomarker**: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results
- **Probable valid biomarker**: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. A probable valid biomarker may not have reached the status of a known valid marker because, for example, of any one of the following reasons:
  - The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.
  - The data elucidating its significance, although highly suggestive, may not be conclusive.
  - Independent verification of the results may not have occurred.

Ref: htpp://www.fda.gov/cder/guidance/6400fnl.pd

The objective is to move from a mechanistic process view (image, pharmacologic process, etc.) towards standards for criteria for validation and the adoption of a common vocabulary to describe the status of a biomarker.

Dr Larry Lesko

Surrogates

3.1.2 Validation of biomarkers and surrogate end-points

There are, as yet, no global 'gold standards' for evaluating biomarkers and there is not even international agreement on criteria. It is generally accepted that a 'light touch' is needed in imposing regulatory regimes but there are different considerations when considering drug-

device combination products or services, because of the need to ensure that IVDs can be used interchangeably.

In order to move forward there must be incentives to carry out validation of surrogates and endpoints with adequate protection of intellectual property, when joint studies are undertaken in consortia. There should be safeguards to ensure that companies do not obtain a 'free ride' on the back of those that contribute work and resources but the larger companies may need to accept that their efforts will help smaller enterprises.

Conditional approvals are a possibility for providing incentives to deliver validation studies in return for earlier access to the market. This, however, needs cooperation and joint involvement between regulatory authorities and bodies responsible for health technology assessment (e.g., NICE in the UK) that influence the payment and reimbursement status of products. Early approval without the prospect of earning a reasonable return on investment will not provide an incentive to use and validate surrogate end points.

Dr David Jefferys

Implications of the FDA classification

The designation, by FDA, of three validation levels: exploratory, probable valid and known valid, has ramifications across the spectrum of drug development from animal testing through clinical development to the use of the product in the marketplace. There are requirements to submit data for 'known valid' biomarkers but data on 'probable valid' markers are only required if it was used in a way that is important to the development programme, for example the selection of patients. Data on observational or exploratory biomarkers do not need to be submitted but is often included for information and education.

Conditional approvals

The US conditional approval system can be seen as providing incentives for companies to validate biomarkers used as surrogate end points. Approval is granted on the condition that the extensive work needed to validate surrogate markers is carried out in after launch (Accelerated approval rule - Subpart H). Early marketing can therefore be achieved but it must be remembered that constraints may be placed on marketing and advertising and that, if the outcome of validation is not satisfactory the approval can be withdrawn without the normal lengthy legal requirements, hearings and procedures.

Gregory Levine

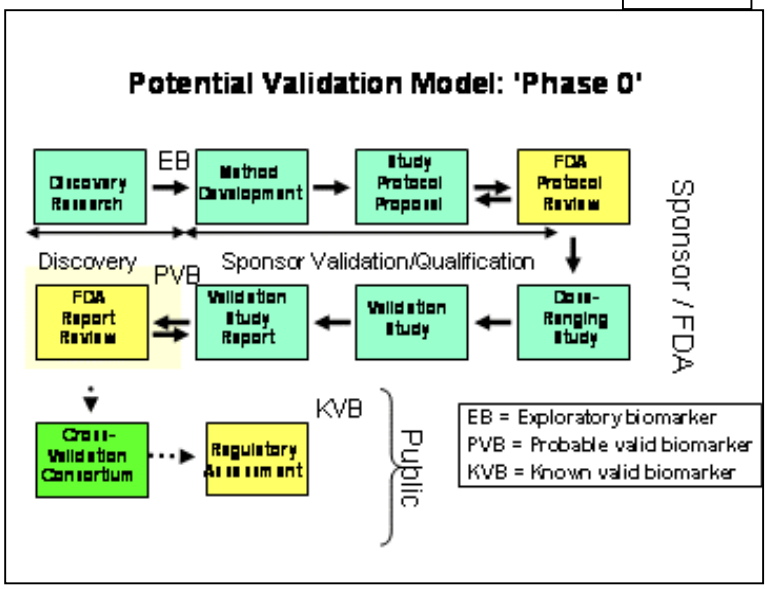
Thoughts on validation

Under UK law, a case in the criminal courts must be proved 'beyond reasonable doubt' whereas a civil case only needs to demonstrate a 'reasonable presumption'. When it comes to surrogate endpoints and the validation of biomarkers, society must decide whether to accept products on a reasonable presumption of efficacy (to be born out later) or take a harder view that efficacy must be proven beyond all reasonable doubt.

Dr David Jefferys

Schematic for the validation of biomarkers

Figure 2



Dr Christopher Webster (with acknowledgement to Dr Gerard Maurer, Novartis)

3.1.3 Surrogate Endpoints

Surrogates

A surrogate endpoint has been defined as 'a biomarker intended to substitute for a clinical endpoint'[2]. They are used by FDA as the basis for accelerated approvals and some ordinary approvals, but also for approval of supplements to approvals.

There is a set of general principles that are applied to candidate surrogates but FDA does not have an inventory of surrogates or a record of the evidence supporting them. Surrogates are used on a case-by-case basis but some historical examples are given in table 3.

Table 3		
Types of Biomarkers	**Surrogate Endpoints**	**Clinical Endpoints**
Physiological	Blood Pressure	Stroke Risk, Reduced Mortality
Pharmacokinetic	Plasma Drug Levels	Equivalent Efficacy and Safety
Pharmacodynamic	Cardiac Output	Symptomatic Relief of Short-term CHF
Imaging	MRI	Recurrence of MS Episodes
Clinical Response	Time to Progression	Survival in Breast Cancer

There is, however, little evidence to support the progression from biomarker to surrogate and to outcome. There is no good database that maps this progress based on historical precedents.

[2] NIH Definitions Group. Biomarkers and Surrogate Endpoints in Clinical Research. In Downing GJ (ed.) 1-9.Clin Pharmacol Ther 2001, 69, 89-95.

Consortia

Critical Path Project

A project has been started to develop a biomarker and surrogate inventory. Firstly (see figure 3), it is proposed that biomarkers should be categorised by disease and questions would be asked (left-hand column) in relation to the adoption of the biomarker as a surrogate endpoint (SE). Next, current surrogate endpoints that are used to support approvals would also be examined asking questions as indicated in the right-hand column.

Figure 3

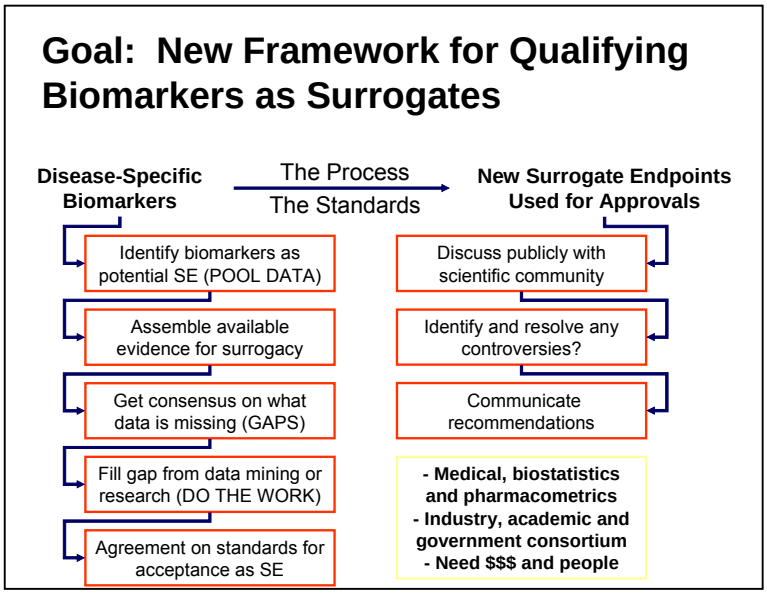
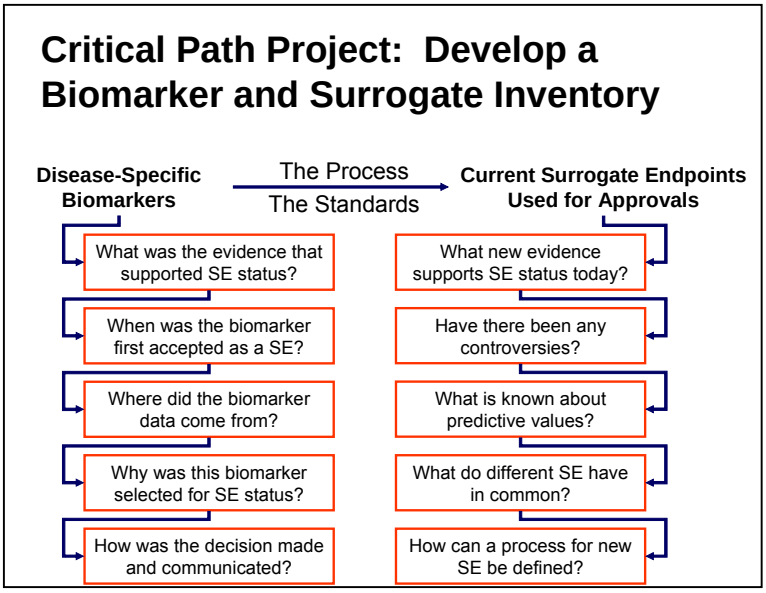


Figure 4



This would map the process by looking at what has already been achieved in order to identify gaps in knowledge about attractive biomarkers that could be surrogates.

Second stage is to set a framework for qualifying biomarkers as surrogates, using the data collected in stage 1 (figure 4). This has to be a collaborative effort between different disciplines and between organisation and it also needs budget and manpower. It is hoped that funding will become available from the Critical Path institute to take this forward.

Dr Larry Lesko

3.2 R&D PROMISES AND PRACTICE

Promises

3.2.1 The promise of Biomarkers

A major factor in the escalating cost of R&D is the number of compounds that fail and are terminated during development. Survival rates in the different Phases of development vary but CMR data has shown that the Phase 2 problem has become worse over the last decade with only 1 in 5 products proceeding to Phase 3.

Whilst expectations of a survival rate of 80-90% would be unrealistic for Phase 2, it should not be as low as 20%. This is the battleground where one finds the true strengths and weaknesses of a compound and biomarkers will help to sort through this process in a more efficient way.

Dr John L LaMattina

3.2.2 Imaging biomarkers

Imaging biomarkers have a pivotal role in neuroscience research, in particular PET (positron emission tomography) and SPECT (single proton emission computed tomography). The different roles are outlined in Table 4

PET neuroreceptor imaging is a complicated venture involving a multidisciplinary approach. With short-lived radioisotopes such as ^{11}C (half-life 20 minutes) it requires an on-line cyclotron at the site of the clinical application. Longer-lived isotopes such as ^{18}F or ^{123}I the agent can be made off-site and this has major implications for the design of a clinical study.

The technique has major clinical applications in product development:

- As an adjunct to dose selection for proof of concept studies;
- As a potential surrogate marker for treatment outcomes:
  - Parkinson's disease imaging targets: surrogate marker for dopaminergic degeneration;
  - PET and SPECT tracers as markers for *in vivo* beta-amyloid load in the brains of Alzheimer's disease patients

Table 4: Functional Neuroimaging in Neuropsychiatry Research

Method	Application
Radioligand	Determine the distribution of that ligand in the brain and other organs
Radioligand in tracer-dose application	Quantitatively analyse the concentration of binding sites in brain and other tissue to make assumptions about the concentration of those sites (= 'binding-potential')
Use of a displacement paradigm to measure the competition of a tracer with a drug for particular binding sites	Assess the relative 'receptor occupancy' of the drug
Simultaneous use of a drug and a tracer with affinity to a different transmitter system	Measure the effect of the drug on a tracer targeting another neurotransmitter systems
Indirect measures of drug action using radio-labels e.g.,[^{3}H]H2O, [^{123}I]HMPAO or [^{18}F]FDG	Measure regional cerebral blood flow or metabolism as an indicator of the action of the drug
Radiolabeled enzyme substrates	Indirect determination of enzyme activity or cerebral metabolism

Summary of the use of neuroimaging in drug development

Radiolabeled tracers for PET or SPECT can be used as biomarkers in drug development to assess:

- The distribution and concentration of a particular target (e.g. neurotransmitter receptor, beta-amyloid plaque, etc.) in the brain or target organ;
- Receptor occupancy of a therapeutic compound by quantitatively analyzing the drug induced tracer displacement from the target and duration of on-target pharmacology
- The distribution of a very low dose (< 1 μg) of a radiolabeled drug (PET micro dosing) to confirm brain penetration (in cases where a specific tracer for a target cannot be found);
- Drug induced changes in brain glucose metabolism (e.g. FDG-PET) or regional cerebral blood flow (HMPAO SPECT) as a proxy for brain activation or deactivation during treatment. Indirect marker of for brain activation or decrease of pharmacologically induced activation during certain treatment paradigms.

Neuroimaging studies can potentially provide evidence that:

- A novel drug reaches a specific drug target in rodents (micro-PET), non-human primates and/or humans;
- A mechanism is relevant to pathophysiology;
- A drug can be used to treat a disease in humans if the biomarker is valid.

Dr Johannes Tauscher

Consortia

3.2.3 Potential and pitfalls of biomarkers in Alzheimer's Disease

Potential biomarkers for the demonstration of pathophysiology and the effect of treatment in Alzheimer's disease (AD) include:

- Soluble biomarkers
  - Aβ fragments in plasma/CSF
- Tissue biomarkers (post-mortem histopathology)
  - Neurofibrillary tangles
- Imaging biomarkers
  - Structural markers
  - Functional/molecular markers

Imaging biomarkers are currently the focus of much attention as they:

- Provide objective and quantitative comparisons of brain structure, function, and pathophysiology both cross-sectionally and longitudinally, in contrast with clinical scales for monitoring disease progress;
- Provide a means of correlating brain pathophysiology with relevant clinical features in the natural history of the disease;
- May allow for sub-stratification or characterisation of more homogeneous subpopulations
- Have the potential to become accepted surrogate markers of meaningful treatment response and dose guidance.

One of the problems of correlating imaging biomarkers with clinical symptoms is that the cognitive assessment scales of the mid-1990s are still being used and these, themselves, have problems. They are not, for example, very sensitive to issues such as quality of life. New technologies are therefore being compared back to old scales.

Another issue is in the interpretation of images in relation to disease progression. A potential target for second and third generation AD product is shrinkage of the ameloid plaques. This may be seen in the imaging as an increase in the volume of the lumen in coronal sections, but this is also a manifestation of disease progression.

Dr David Jefferys

3.2.4 Keeping the 'information content' of biomarkers in proportion

Referring to the 'Geoffrey Rose paradox' it can be seen that, when it comes to actionable health information, there is a dramatic difference between public health and individual patient-related health decisions. In relation to public health, the informational content of a marker can be modest and have major impact. For example, a marker may provide a mere 1% better outcome but, once multiplied by millions of patients, the outcome is dramatic. Provided there is a good enough P value, the magnitude of the effect is not important.

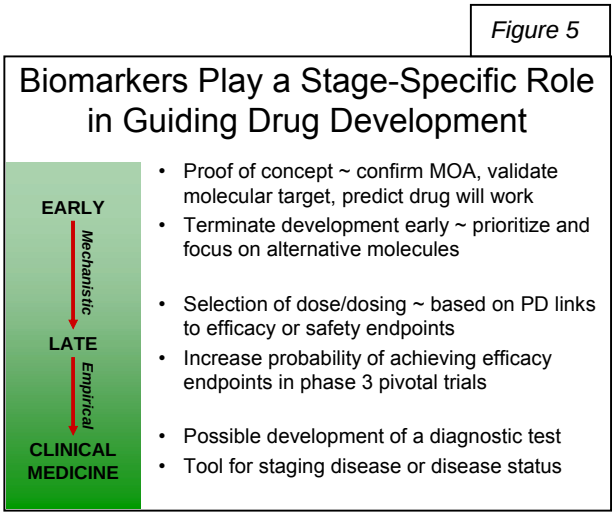
When it comes to taking care of individual patients, however, it is the magnitude of the effect that is important and one is much more demanding that the patient's health will not be risked by using a marker that is only marginally better than by taking no action.

Prof. Klaus Lindpaintner

3.4.6 Biomarkers and labelling

Biomarkers are used throughout the drug development process and ultimately in clinical medicine (figure 5). There is an early emphasis on mechanistic factors and biomarkers that guide dose selection and trial design but in later development these are 'forgotten' because they rarely appear in the label. The later clinical trials are, for example based on a single or two doses that are approved and appear in the label. There is therefore a large amount of information that is lost and there is a major opportunity to enhance labelling by referring to biomarkers more appropriately and hence allowing physicians to distinguish between different patients when using the product.

Figure 5



Dr Larry Lesko

3.4.7 Target product profiles for biomarkers as diagnostics

When it comes to the development of new molecular entities, the whole issue of target product profiles is very much to the fore but it is conspicuously absent from the development of biomarkers and the same is true for the criteria that need to be met. Each tends to be dealt as an individual case but it is fundamental to making progress to look at the prognosis for a marker before investing in an expensive development strategy.

Highly sensitive, specific markers are needed in order to make treatment decisions and avoid adverse events. A marker for adverse events needs to have high specificity whilst sensitivity is less important. If the marker is not very specific one may deny patients a potentially life-saving medicine on the off chance that they will have a serious side effect when it might be more important to take that risk rather than withhold a potential benefit of the medicine.

On the contrary, a highly sensitive marker is needed for a life-threatening condition, in order to predict efficacy, and ensure that a potentially life-saving treatment is not denied to responders. The situation changes again, however, for more trivial diseases where the efficacy marker must be very specific and the side effect marker very sensitive.

Prof. Klaus Lindpaintner

3.5 SAFETY ISSUES

Risk management

3.5.1 Risk Management

FDA has set out principles and policies on Risk Management in guidances, acknowledging the fact that no product is completely safe but trying to find a balance where products have specific safety issues but also have unique benefits. The challenge is to allow that product on the market and manage the risk in a way that is acceptable to patients and the public and does not intrude on healthcare delivery.

Biomarkers have a role in establishing risk action plans by targeting therapy to responders and excluding those at higher risk of adverse events. The wide range of tools for implementing such plans range from the informational (professional and patient labeling, training and education) to the interventional (recording and attesting that requirements have been satisfied before the product is made available).

In legal terms, risk management cannot be separated from product liability. A liability case will centre on the question of whether the company acted 'reasonably' to ensure that physicians and patients comply with labeled pharmacogenomic tests and applied appropriate diligence. There are also questions of 'tort' law, in relation to liability and whether companies can be held to a higher standard of diligence than the specific regulatory conditions agreed under the product approval

Unlike other aspects of regulation, risk management plans should not, therefore, be regarded as a 'negotiation' with regulators in order to arrive at a strategy that provides the minimum limitations on marketing. From a legal viewpoint, this can create a record of reluctance to adopt risk avoidance measures that can subsequently be revealed in the event of a law suit at a later stage.

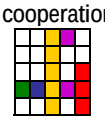
Examples of theories on which an individual or class action may be taken include:

- Failure to warn: allegations that the company knew more than it was prepared to reveal to physicians and public;
- Incorrect dosing: Assertions that the company could have developed a biomarker test to guide dosage selection where this is critical;
- Ineffective treatment when an alternative was available: Allegations that the company did not do enough to develop or make available a test to identify responders;
- Economic harm: Suits brought by patients or payers alleging overpayment for ineffective or unsafe treatment.

The message is not, however, to avoid the use of biomarkers but to adopt the new science in a way that shows that the company has been diligent and wishes to improve patient care and safety by ensuring that the right people are on the treatment. It is also important to be candid and cooperative with the regulators. In this way liability risks can be reduced and mitigated, if not eliminated, in today's legal environment.

Gregory Levine

Patient cooperation



3.5.2 Ethics of testing clinical samples retrospectively

When safety issues arise after authorisation there is tacit obligation on companies to carry out further investigations which may include further testing of retained clinical samples. FDA has raised concerns over informed consent since samples provided for one purpose, with consent concern were then used for another purpose – e.g., retrospective analyses - without the specific consent from patients.

A guidance was, therefore, issued in April 2006 entitled:

> Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff

Reference: http://www.fda.gov/cdrh/oivd/guidance/1588.html

This discusses how to use left-over samples and 'de-identify' them for future use, since some of the medical conditions can be very rare.

IRB: Consent from an institutional review board is required;

Stability: If samples have been frozen, proof will be needed that the samples are still stable and that the potency of the marker has not been lost;

Testing protocol: Whether there a set protocol among the different sites that will carry out the testing in order to reduce variability;

Tissues: Consistency between the way in which tissues are read and, in the case of tumours, whether samples should be restricted to large tumour masses rather than small, early tumours

Dr Joe Hackett

4 MEDICINES AND DEVICES IN COMBINATION

4.1 CO-DEVELOPMENT

4.1.1 Drug and in vitro diagnostic (IVD) developed in parallel

Drug-IVD combos

Sometimes the FDA will say that an available test is needed when they approve a drug. For example, if a certain patient population has been excluded from clinical studies because of adverse reactions, a suitable test to exclude susceptible patients must be available once the drug is approved. It is the responsibility of the Center for Devices (CDRH) to approve such tests.

The different scenarios for drug-device co-development are given in table 5

Table 5: Drug/device development scenarios

Within one company
Pharmaceutical firm develops both the new product and IVD
- Products co-developed with full access to patient samples

'Ideal' solution for the agency

Outside IVD manufacturer 1
Pharmaceutical company manufactures the drug but not the IVD
- Timing can be problem if the test is not already marketed: approvals must coincide
- Does the IVD firm have access to drug study blood samples?
- Are second and third IVD firms also given access? There may be problems with availability of adequate samples and consequent delays.

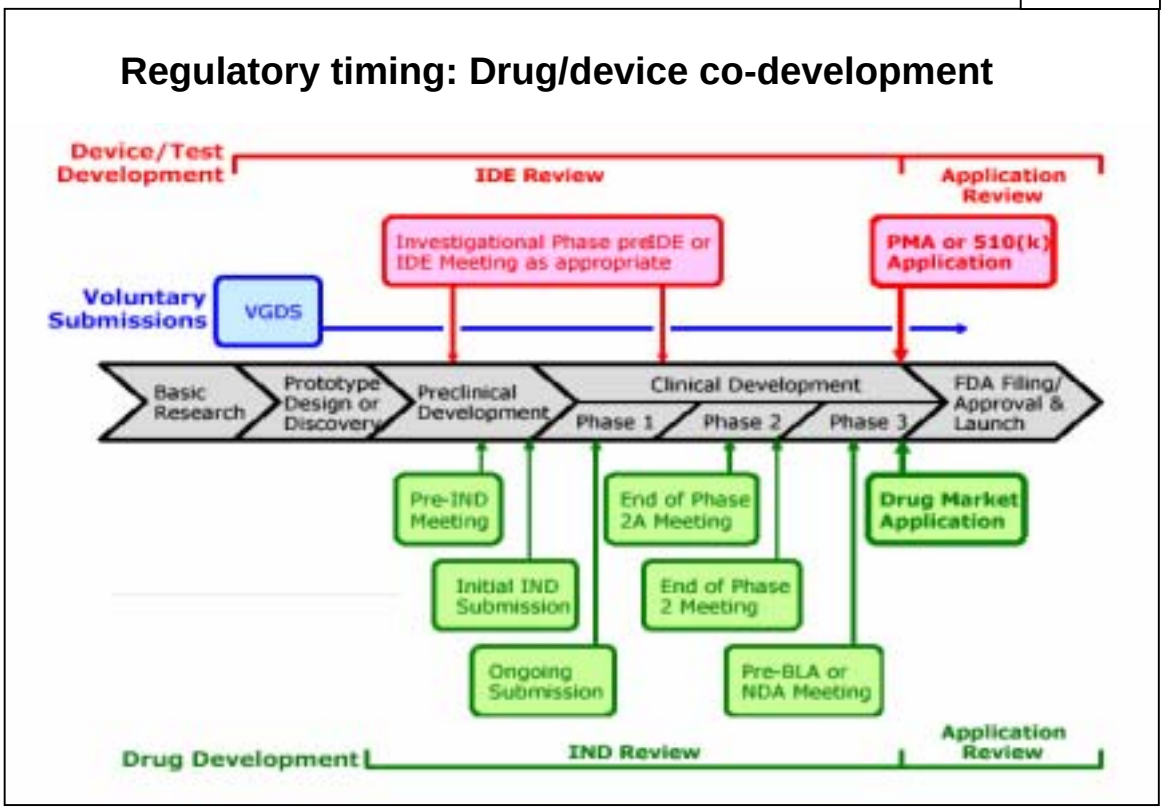
Outside IVD manufacturer 2
Pharmaceutical company manufacturers the drug and has developed a biomarker but does not manufacture IVDs
- IVD company has a head start but who is responsible for the validation?
- Issues of access to blood samples, as above

New test for an old product
An IVD company develops a test for a product that a company is already marketing. Will the latter be interested?
- If yes. Will they be willing to share samples and will these still be available?
- If no, the IVD company will need to undertake new studies

Drug-IVD combos

FDA has published a concept Paper o drug-diagnostic co-development that can be found at: http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf that includes the diagram on timing shown in figure 6.

Figure 6



The Office of in vitro diagnostics (OVID) describes this as reflecting 'preliminary Agency thoughts on how to how to prospectively co-develop a drug or biological therapy (drugs) and device test in a scientifically robust and efficient way'.

Key issues for development of an IVD

FDA is conscious of the need to review diagnostics efficiently and in a timely manner in order to ensure that availability of the final product is not delayed. Issues of particular concern are:

- **Reproducibility and Validation:** Whether there is uniformity not only between different units in a lot but also between different lots, and between laboratories and facilities performing the test;
- **Lack of Standardisation**: This has implications in data mining (Bioinformatics) and also in that extrapolation from different platforms/genes give different answers:
  - This is being addressed as standards are developed and evaluated and further proposals should be available soon
- **Manufacturing Controls**: Some IVD manufacturers are small and not familiar with the Agency's CMC requirements for authorisation of a diagnostic.

Informal advice IVD development

CDRH has set up procedures, similar to those for drug products that allow informal discussions between a diagnostic manufacturer and FDA. The manufacturer can obtain advice on proposals or protocols. There is usually no formal investigational device exemption (IDE) but there can be informal agreement on how to develop a pre-market notification - 510(k) - for Class 2 devices or pre-market approval (PMA) for Class 3 devices.
Before the study starts advice will be given on whether the protocol is acceptable for gathering and analysing the information needed to place the IVD on the market but this is, of course no guarantee of the outcome.

Dr Joe Hackett

4.1.2 Public Policy: Incentives to develop drug-diagnostic combinations

The future vision of 'personalised medicine' depends upon the development of biomarkers, most often in the form of in vitro diagnostic (IVD) agents that will identify responders and/or exclude those susceptible to adverse reactions. These will either be co-marketed with the therapeutic product or may be available as separate commercial products.

Incentives to develop such products will, however, have implications for public policy:

- Flexible and value-based pricing and reimbursement for diagnostics could provide drug and diagnostic manufacturers with a stronger incentive to evaluate the business case for linked diagnostics and therapeutics during drug development;

Incentive-oriented reforms--linking pricing and reimbursement for drugs and diagnostics to value creation--will encourage personalized medicine.

- A strong, consistent, predictable IP environment remains key to the innovative development of pharmaceuticals but there are issues related to the way content *vs*. platform protection is resolved in diagnostics that will affect long-term business prospects.
- Public policy should not focus on pharmacogenomic technologies alone, but should consider the broader paradigm of linked diagnostic-therapeutic agents and consider the biomarkers from a more general perspective.

Dr Lou Garrison

4.1.3 A legal perspective

Labelling issues

Complex issues arise in relation to labelling for example whether a specific diagnostic will be mentioned and how the label will be negotiated if two different companies are involved. If a change is made to the diagnostic will the drug manufacturer be adequately in formed and will the diagnostic need to be validated again?

Generic products: development of diagnostics for clinical practice

If a generic product is on the market, is there an incentive for a pharmaceutical company to develop a diagnostic? A project has been announced under the Critical Path Initiative to develop a diagnostic test to help determine the optimal dose for warfarin. It is unlikely that any manufacturer of the products that are widely available as generics, would have an interest in leading such an undertaking and the role is likely to fall to an academic institution working with FDA. The ultimate goal would be to the new dosing information into the labelling of products, on a mandatory basis.

Use of the diagnostic: Who is responsible for monitoring?

If a test is available in relation, for example, to susceptibility to adverse reactions there are questions about the responsibility for monitoring the use of the diagnostic. Does this responsibility rest with the company, with the physicians or, to some extent, with the patients themselves?

There has already been a test case where it was claimed that the company, notwithstanding label warnings and 'Dear doctor' letters, had failed to take adequate steps to ensure that patients at risk of an adverse effect were adequately tested.

Gregory Levine

4.1.4 Personalised medicine: the commercial and economic rationale

Economics

Linking a pharmacogenomic or other biomarker (diagnostic Dx) to the use of a therapeutic agent (Tx) could create additional economic value in at least four ways:

- **Reduced adverse events:** Removing the non-responders or poor responders from the pool of users means that their costs, in monetary terms and in relation to negative utility and adverse events are avoided;
- **Greater volume of adoption:** Better targeting can lead to increased use by good responders, some of whom would not have used the drug previously;

- **Improved compliance:** Good responders are more likely to be compliant and will gain additional net benefits, especially for long-term chronic therapies.
- **Less uncertainty:** The improvement of predictability of outcomes creates additional value for patients in reducing the uncertainty factor.

Given current pricing and reimbursement structures, (see table 6) however, it is widely recognised that a therapeutic manufacturer has a very limited financial incentive to invest in developing a diagnostic for pharmaceutical products already on the market, since the result would be to restrict the size of the market.

Understandably, most of the economic evaluation work in this area has focused on existing products rather than pharmaceuticals in development.

Table 6: Comparative economic considerations

Prescription Pharmaceuticals	Diagnostics
Current business model Intellectual property protection High margins/high risk Blockbuster financing Detailing/promotion	***Current business model*** • Low margins • Compete on platform • High volume sales
Pricing and reimbursement Patents confer some degree of monopolistic power but there is the countervailing monopolistic power of buyers: • Governments exert this by mandating price controls on new drugs. • Major types of price controls are: therapeutic group reference prices, and international price referencing. The major exceptions ("free pricing" environments) have been U.S., Germany, and the UK Outside the US (a 'free pricing' environment). companies have little latitude to increase price after a product is on the market. Initial price negotiations are therefore critical for capturing any additional value created by innovation.	***Pricing and reimbursement*** Compared to pharmaceuticals, competitive entry for a given product is easier, and pricing and reimbursement are more controlled in most markets. Reference pricing is common, especially in EU. Reimbursement is linked by reference to existing tests using 'cross-walking' and 'gap-filling' criteria Little consideration is given to the extra value provided by a new test, although health economics arguments are increasingly requested.

Economics

Economic models

A simple economic framework can be used to explore the incentives under different scenarios in which a new therapeutic product (Tx) is marketed with and without a diagnostic test (Dx) that accurately predicts responders and provides the possibility of screening all patients and treating only those that are likely to respond.

In this framework, the economic 'value' of a medicine is the amount that fully informed patients would be willing to pay (WTP) based on:

- Any cost savings;
- Life years gained;
- Improvements in quality of life or morbidity;
- Reduction in uncertainty.

It is important to note that the total value created is actually larger due to the additional reduction in uncertainty arising from the linked Dx-Tx. In principle, the total WTP to should be greater, so that the Tx manufacturer would not necessarily receive less revenue if the marker were restricted to the subset of identified responders.

However, how this total value is allocated in the real world will depend on the several factors:

- Whether the Tx is already on the market with a price when the Dx enters.

- Whether Tx and Dx pricing and reimbursement systems are flexible and value-based (rather than cost-based).
- The strength of patent protection on the Tx and Dx.
- Whether the Tx company also markets the Dx.
- Whether there is a single government payer or a competitive private health insurance market.

Dr Lou Garrison

Abbreviations

AD	Alzheimer's disease
ADNI	Alzheimer's disease neuroimaging initiative
BM	Biomarker
CRADAS	Cooperative research and development agreements
CYP 450	Cytochrome P450
DCE	Dynamic contrast enhanced (MRI)
EGFR	Epidermal growth factor receptor
FDG	Fluorodeoxyglucose (PET)
FNIH	Foundation for the National Institutes of Health
FP7	EU Seventh framework programme for research
GIST	Gastrointestinal stromal tumours
IDE	Investigational device exemption
IPRG	Interdisciplinary pharmacogenomics review group
IVD	In vitro diagnostic
MBDD	Model based drug development
MRI	Magnetic resonance imaging
NET	Norepinephrine transporter
NIH	National Institutes of Health
OA	Osteoarthritis
PET	Positron emission tomography
PFE	Pfizer Inc. (stock symbol)
PGx	Pharmacogenomics
PMA	Pre-market approval (medical devices) – also known as a 510(k)
SPECT	Single proton emission computed tomography
VGDS	Voluntary genomic data submission