Qualification and Use of Biomarkers in Drug Development: Existing Frameworks

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PhRMA PISC Biomarkers Working Group
Pfizer Regulatory Strategy & Policy

Institute of Medicine Workshop on Biomarker Qualification
6 April 2009
Biopharma Perspective on Biomarker Development

- Biopharma recognizes the need for the development, validation and qualification of biomarkers in order to
  - facilitate translational research
  - improve productivity of drug development and
  - speed the delivery of safe and effective treatments to patients
PhRMA Biomarkers Working Group

Recent Activities:

- Pharma Company representatives met to discuss concept/context of Biomarker Qualification (April – October 2007)
- Workshop co-sponsored with FDA to discuss concepts (July 2007)
  - Case studies presented and discussed
  - Alignment of FDA and WG thinking

  - **Manuscript to capture Workshop concepts (August-Sept 2007)**

  - **2nd Manuscript to test concepts with case studies (in progress)**
    - “The Value, Qualification and Regulatory Use of Surrogate Endpoints in Drug Development” Clin Pharm Therap 2009 (submitted)
Examples: Global Biomarker Policy Activity

- **PDUFA IV “Expediting Drug Development” Objectives**
  - "FDA will participate in workshops with representatives from the scientific community (including industry, academia and other interested stakeholders) to further the science toward development of guidance documents"

- **EMEA Draft Guidance “Biomarker Qualification: Guidance to Applicants”**
  - issued April 2008, comments thru June 2008, CHMP final 22 Jan 2009

- **Critical Path Institute/Predictive Safety Testing Consortium**
  - preclinical nephrotoxic biomarkers FDA endorsed qualification (April 2008)

- **EC Innovative Medicines Initiative: Translational Biomarkers**
  - focus on organ toxicity markers and disease mapping markers

- **ICH E16 Proposal and Discussion June 2008 - ongoing**
  - Harmonize genomic biomarker data submission and content across regions

- **Kennedy-Hutchinson “21st Century Cancer ALERT Act”**
  - introduced 26 March 2009, extensive discussion on role of biomarkers
EMEA ‘BMQT’ & qualification process outline*

*does not address evidentiary standards for biomarker qualification
PhRMA Biomarkers WG: Proposed New Objectives

Discuss & compare PhRMA Member experience & perspective
- Policy-level engagement
- Consolidate common ground; “PhRMA position statements”
- Build on success of the Biomarkers Consortium & others

Continue to develop concept and context for biomarker qualification
- Partner with FDA & other institutions to advance common solutions
- Align current and future global regulatory guidance and practices
- Assemble and submit PhRMA comment to emergent guidance

Partner with other groups (e.g. Genomics Technical Group)
- Foster alignment across Biomarker arena, minimize redundancy

Sunset or Re-charter when objectives achieved

Out of Scope:
- technical aspects of biomarker validation & qualification
- "platform" specific aspects of validation & qualification
Sharing Biomarker Information

- Biopharma companies partner with other companies, research groups, institutions etc…and share unpublished and/or proprietary biomarker data, knowledge, assays, technologies or samples when collaborating entity has complementary resources and the combined resources facilitate biomarker validation at lower cost. This may be done via individual collaboration or consortium basis.

- The Biopharma Industry recognizes Critical Path and Innovative Medicines Initiative as important developments and is active in supporting efforts to ensure their success.

- Active examples of industry-academic-govt consortia:
  - Biomarker Consortium [http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml]
# Major Public-Private Partnerships

<table>
<thead>
<tr>
<th>Partnership</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Grand Challenges in Global Health</td>
<td>$200M</td>
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<tr>
<td>Partner: Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>Collaboration for AIDS Vaccine Discovery (CAVD)</td>
<td>$33M</td>
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<tr>
<td>Partners: VRC/NIAID, Bill &amp; Melinda Gates Foundation</td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s Disease Neuroimaging Initiative (ADNI)</td>
<td>$27M</td>
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<tr>
<td>Partners: NIA &amp; AstraZeneca, Bristol-Myers Squibb, Eisai, Elan, GE Healthcare, GlaxoSmithKline, Innogenetics, Eli Lilly, Merck, Novartis, Pfizer, Schering-Plough, Synarc, Wyeth Alzheimer’s Association, Institute for the Study of Aging</td>
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<tr>
<td>Genetic Association Information Network (GAIN)</td>
<td>$26M</td>
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<tr>
<td>Partners: NHGRI, NLM &amp; Pfizer, Affymetrix, Broad Institute, Abbott Laboratories</td>
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<tr>
<td>Observational Medical Outcomes Partnership</td>
<td>$21M</td>
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<tr>
<td>Partners: FDA, sixteen biopharmaceutical companies</td>
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<tr>
<td>Osteoarthritis Initiative (OAI)</td>
<td>$18.5M</td>
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<tr>
<td>Partners: NIAMS &amp; Pfizer, Novartis, Merck, GlaxoSmithKline</td>
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<tr>
<td>Avon-NCI Progress for Patients Award Program</td>
<td>$12M</td>
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<tr>
<td>Partners: NIAMS &amp; Pfizer, Novartis, Merck, GlaxoSmithKline</td>
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<tr>
<td>The Biomarkers Consortium</td>
<td>$11.3M*</td>
</tr>
<tr>
<td>Partners: NIH, FDA, CMS, PhRMA, BIO, pharmal/biotech companies, non-profits</td>
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</table>
# Biomarkers Consortium Contributing Members (60)

## For-Profit Companies (27)
- Abbott Laboratories
- Althea Technologies
- AstraZeneca
- Avalon Pharmaceuticals
- BG Medicine
- Boehringer-Ingelheim Pharmaceuticals
- Bristol-Myers Squibb
- Digilab Biovision GmbH
- EMD Serono
- Genstruct
- GlaxoSmithKline
- GVK Biosciences
- InfraReDx
- Ingenuity Systems
- Johnson & Johnson
- Eli Lilly and Company
- Luminex Corporation
- Lundbeck
- Merck and Co., Inc.
- Metabolon
- Novartis
- Novo Nordisk
- Pfizer Inc
- F. Hoffmann-La Roche
- Rules-Based Medicine, Inc.
- Scout Diagnostics
- Wyeth

## Nonprofit Organizations (33)
- Academy of Molecular Imaging
- Advanced Medical Technology Association
- Alliance for Aging Research
- Alzheimer’s Association
- American Association for Cancer Research
- American Cancer Society
- American College of Neuropsychopharmacology
- American Health Assistance Foundation
- American Society for Clinical Pharmacology and Therapeutics
- American Society for Therapeutic Radiology and Oncology
- American Society of Clinical Oncology
- Association of Clinical Research Organizations
- Autism Speaks
- Battelle Memorial Institute
- Biotechnology Industry Organization
- Cystic Fibrosis Foundation Therapeutics
- Federation of Clinical Immunology Societies
- The Hamner Institutes for Health Sciences
- High Q Foundation
- Immune Tolerance Institute
- Polo Ralph Lauren Foundation
- Juvenile Diabetes Research Foundation
- Kidney Cancer Association
- The Leukemia and Lymphoma Society
- Lupus Foundation of America
- Lupus Research Institute
- Michael J. Fox Foundation for Parkinson’s Research
- Ontario Cancer Biomarker Network
- Pharmaceutical Research and Manufacturers of America
- Radiological Society of North America
- Ryan Licht Sang Bipolar Foundation
- Society of Nuclear Medicine
- Vanderbilt University
The Biomarkers Consortium Governance

The Biomarkers Consortium Executive Committee
[NIH / FDA / CMS / industry / general public / Foundation for NIH]

- Cancer Steering Committee
- Metabolic Disorders Steering Committee
- Neuroscience Steering Committee
- Inflammation and Immunity Steering Committee

Project Team 1
Project Team 2
Project Team 3
Project Team 4
Project Team 5
Project Team 6
Definitions - Biomarkers and Surrogate Endpoints

- **Biomarker**
  - A characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. (NIH Workshop definition).
  - "Almost anything you can measure"

- **Surrogate endpoint**
  - A biomarker that is intended to substitute for a clinical endpoint'......[a] surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence (NIH Workshop definition).
  - “Evidence accepted by stakeholders in lieu of disease outcome data"
Distinguishing Validation from Qualification

Validation

Method validation is the process of assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data.

- The biomarker literature occasionally uses "validation" and "qualification" or "evaluation" interchangeably.
- Validation and qualification processes are distinct.
- "validation" does not include or describe the qualification process.

Biomarker Qualification: proposed definition

**Qualification**

- Biomarker qualification is the evidentiary process of linking a biomarker with biological processes and clinical or disease endpoints.
  - A biomarker is qualified when there is sufficient evidence to accept as fit for a defined purpose in a specified context
  - Biomarker qualification requires evidence linking a biomarker with disease biology & clinical endpoints, yet remains dependent on the intended application
  - Based on these considerations, a given biomarker may be considered “validated” in terms of assay or test performance, but would not be considered “qualified” until it had been assessed relative to a specific application.
  - Likewise, a given biomarker could be considered “qualified” for one specific application but not “qualified” for another

# Classifying Biomarkers for Drug Development

Biomarkers as applied to the drug development process can be classified in two dimensions,

(i) the type or purpose of the biomarker and
(ii) the degree of linkage of the biomarker to efficacy or safety outcomes.

<table>
<thead>
<tr>
<th>Biomarker Types (eg)</th>
<th>Linkage to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Target</td>
<td>Low – Medium - High</td>
</tr>
<tr>
<td>• Mechanism</td>
<td></td>
</tr>
<tr>
<td>• Functional outcome</td>
<td></td>
</tr>
<tr>
<td>• Surrogate outcome</td>
<td></td>
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<tr>
<td>• Safety</td>
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</table>
Biomarker Linkage to Outcome: Triage?

**LOW** – there is no consistent information on the linkage of biomarker change to efficacy or safety in humans. Linkage to outcomes in animal models may exist. Biological relevance unknown or not clear.

**MEDIUM** – Biomarker differences are associated with efficacy or safety outcomes data in humans, but association has not been reproducibly demonstrated in clinical studies. Biology relevant but pathway not known.

**HIGH** – Biomarker differences have been reproducibly demonstrated to be correlated with and biologically related to efficacy or safety outcomes in two or more adequately powered clinical trials.
Application of biomarkers

Internal decision making
Assess safety/efficacy
Regulatory approval

Phase I
- Proof of pharmacology/mechanism
- Proof of efficacy/proof of concept

Phase II
- Evidence of differentiation
- Surrogate end point

Phase III
- Personalised medicine (diagnostic / PGx test)

↑ Weight of evidence
# Stages of Biomarker Qualification

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
<th>Drug development use</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exploration</strong></td>
<td>Research and development tools accompanied by <em>in vitro</em> and/or preclinical evidence, but no consistent information linking the biomarker to clinical outcomes in humans. Corresponds to &quot;exploratory biomarker&quot; in nomenclature suggested by FDA</td>
<td>Hypothesis generation</td>
<td>Gene expression</td>
</tr>
<tr>
<td><strong>Demonstration</strong></td>
<td>Associated with adequate preclinical sensitivity and specificity and linked with clinical outcomes, but not reproducibly demonstrated in clinical studies. Corresponds to &quot;probable valid biomarkers&quot; in nomenclature suggested by FDA</td>
<td>Decision-making, supporting evidence with primary clinical evidence</td>
<td>Adiponectin</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Associated with adequate preclinical sensitivity and specificity and linked clinical outcomes in more than one prospective clinical study in humans. Corresponds to &quot;known valid biomarkers&quot; in nomenclature suggested by FDA</td>
<td>Decision-making, dose finding, secondary/tertiary claims</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td><strong>Surrogacy</strong></td>
<td>Available data demonstrates that the biomarker can substitute for a clinical endpoint. Designation of &quot;surrogate end point&quot; requires agreement with regulatory authorities</td>
<td>Registration</td>
<td>Hb A1C</td>
</tr>
</tbody>
</table>

Biomarker Qualification Discussion Points

PhRMA Biomarkers Working Group:

A consistent framework for the acceptance and qualification of biomarkers for regulatory use would facilitate innovation, enable more efficient research and expand subsequent application of biomarkers in drug development.

Opportunities:

- Consensus from regulators on performance standards for qualification of novel biomarkers
- Involvement of biomarker technical experts in product review committees
- Creation of advisory committees outside individual drug development programs for the specific purpose of considering biomarker acceptance
- Development of a “biomarker label” that specifies accepted uses for specific purposes
- Creation of a safe-harbor forum or process to facilitate the evaluation of immature biomarkers and to encourage innovation
## Biomarker Qualification Evidence Map* (e.g.)

### Fit for Purpose Biomarker Evidentiary Standards: Mechanism Biomarker

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>“Grade D”</th>
<th>“Grade C”</th>
<th>“Grade B”</th>
<th>“Grade A”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological plausibility</td>
<td>Observed assoc. only, literature supportive</td>
<td>Direct evid. of assoc., relevance in animals</td>
<td>Lit &amp; direct evid. in humans, unclear causality</td>
<td>Causality estab in humans, direct pathway linkage</td>
</tr>
<tr>
<td>Interxn with target/mech</td>
<td>In vitro binding data, non-human reagents</td>
<td>In vivo binding in animals, site relevance</td>
<td>In vitro or in vivo binding in human tissue</td>
<td>Human binding &amp; fxnl evidence of pathway response</td>
</tr>
<tr>
<td>Linkage to clin outcome</td>
<td>Epi data assoc. with outcome, non-intervention</td>
<td>Interventional clin data assoc with outcome response</td>
<td>As lower, plus clin evid from same/similar drug class</td>
<td>Consistent link cross class, in majority patients</td>
</tr>
<tr>
<td>Test accuracy, performance</td>
<td>Single lab, non-validated assay</td>
<td>Multi-lab, variance &amp; concordance estimated</td>
<td>As lower, plus variance sources known, controlled</td>
<td>Performance &amp; variance known, standards defined</td>
</tr>
</tbody>
</table>

Combined Solutions

- Regulatory Review Framework for Biomarkers
- Industry-Regulatory-Public Research Consortia
- Biomarker Qualification Standards/Guidance

- Evolution of Biomarkers to Surrogates
- Lower Cost/Risk of Qualification
- Optimize Regulatory & Scientific Acceptance
- Consistent Quality of Measurements
- Enable Personalized Medicine
Example: Gleevec & CML

PC+ Individuals carry gene for fusion protein BCR-ABL

Activated bcr-abl is both a disease biomarker and a drug response biomarker
Evolution of a biomarker (and a drug)

- 1960: Philadelphia chromosome described in CML
- 1984: brc-abl protein identified as possible cause of CML
- 1987: brc-abl characterized as activated tyrosine kinase
- 1990: brc-abl gene shown to produce CML in mice
- 1992: ST1517 (gleevec) selected as TK inhibitor
- 1993: gleevec activity confirmed in mice
- 1999: gleevec activity demonstrated in human CML
- 2001: April, Druker et al. publish results in NEJM
- 2001: Single larger trial released, confirms efficacy
- 2001: May 15, FDA approves gleevec for CML

“Gleevec has converted a once fatal disease into a chronic illness”
Biomarker predicts response & outcome

Figure 2: Patients with a Major Cytogenetic Response.
The percentage of cells in metaphase positive for the Ph chromosome (in bone marrow) and the number of days that the patients received STI571 are shown. Each line represents the cytogenetic response for an individual patient.

Example: Irinotecan (Camptosar)

Pro-drug: Irinotecan

Liver cell:
- Irinotecan
- SN-38
- SN-38G
- CES1
- CES2
- BCHE
- ABC1
- APC
- M4
- CYP3A4
- CYP3A5
- UGT1A1
- CES2
- ABCG2
- NPC

Intestine:
- Irinotecan
- SN-38
- SN-38G
- CES1
- CES2
- BCHE
- ABC1
- APC
- M4
- CYP3A4
- CYP3A5
- UGT1A1
- CES2
- ABCG2
- NPC

Clearance pathway:
- SN-38G
- UGT1A9
- UGT1A6
- UGT1A1
- SN-38

Active form, Topo 1 inhibition:
- SN-38G

Via bile:
- SN-38G
Pharmacogenetic Hypothesis

A toxic response (neutropenia) to irinotecan is due in part to individual variation in activity of UGT1A1 via genetic polymorphisms

The cascade:

- *Iff 7/7* UGT1A1 genotype (*28 variant*)
- enzyme expression ↓
- glucuronidation of the active SN-38 ↓
- exposure to active SN-38 ↑
- toxicity ↑
## Published Data on UGT1A1 & Grade 4 Neutropenia

<table>
<thead>
<tr>
<th>Author</th>
<th>( n/N ) (%)</th>
<th>( 7/7 )</th>
<th>( 6/6 + 6/7 )</th>
<th>Est. Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlini(^a)</td>
<td>0/6 (0%)</td>
<td>21/58 (36%)</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Innocenti</td>
<td>3/6 (50%)</td>
<td>3/53 (6%)</td>
<td>16.7</td>
<td>2.3 – 120.6</td>
<td></td>
</tr>
<tr>
<td>Marcuello(^b)</td>
<td>1/10 (10%)</td>
<td>2/85 (2%)</td>
<td>4.6</td>
<td>0.4 – 56.0</td>
<td></td>
</tr>
<tr>
<td>Rouits</td>
<td>4/7 (57%)</td>
<td>10/66 (15%)</td>
<td>7.5</td>
<td>1.4 – 38.5</td>
<td></td>
</tr>
<tr>
<td>Ando(^c)</td>
<td>4/7 (57%)</td>
<td>22/111 (20%)</td>
<td>5.4</td>
<td>1.1 – 25.9</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Gr 3 or 4 diarrhea or neutropenia

\(^b\) Gr 4 values from personal communication. Published values are 3+.

\(^c\) Gr 4 leukopenia and/or Gr 3+ diarrhea.
Risk of G4 Neutropenia for UGT1A1*28 Genotypes

Based on Rouits (2004)

- **7/7** Frequency: 9%
  - Severe Neutropenia: 57%
  - Efficacy ???
- **6/7** Frequency: 47%
  - Severe Neutropenia: 20%
  - Efficacy ???
- **6/6** Frequency: 41%
  - Severe Neutropenia: 10%
  - Efficacy ???

Severe Neutropenia Incidence: 19%

*Is this sufficient evidence to drive medical practice?*
Camptosar / UGT1A1 Summary

- Evidence of association insufficient to provide a robust predictor of patient outcome or benefit/risk
  - Clinical utility of testing for UGT1A1 status has not been established
  - Effect on efficacy in variant pop. has not been established
  - ID risk of variant population but not individual risk

- Results of newer studies suggest that in lower dose irinotecan combination regimens, 7/7 genotype predictive value is lower than earlier estimates based on single agent (300-350 mg/m²)
  - Innocenti (n=50) – 50%; N9741 (n=497) – 18%; Aviano (n=250) – 5.3%

- UGT1A1 “biomarker” not qualified for purpose of determining dose or dose adjustment – may be ‘plausible’ but not evidence based without prospective studies
  - Unqualified marker initially in label for “safety”, excluding some patients
  - Label later modified to note risk but not prescribe dosing practice
Exploration - Gene Expression in Rheumatoid Arthritis

- Gene expression profiling may be used to:
  - Discriminate between RA and non-RA subjects [linkage to outcome biomarker]
  - Confirm the treatment mechanism [mechanism biomarker]
- But:
  - What do changes actually mean? [relationship with disease outcome is unknown, biological interaction between genes is not understood]
  - What is the false positive rate – even for target/mechanism?
  - How will model developed retrospectively perform prospectively?

Expression of Different Genes at Baseline, 3 and 6 months of Anti-TNF therapy in Circulating Blood Neutrophils
Applying Genomic Biomarkers to RA Development

**Typical DMARD Development Paradigm**

- **FIH/SDT**
- **MDT/POM**
  - Ph Ib/IIa 2-4 wk safety
  - PK/DDI RA
  - Ph II/POC 12-wk RA

3+ years to POC
13-week toxicology studies required for POC studies
Extremely competitive landscape for recruitment of subjects

**‘Enhanced’ DMARD Development Paradigm**

- **FIH/SDT**
- **MDT/POM**
  - Ph Ib/IIa 2-4 wk POC Safety/PONV in RA

Sensitive & objective biomarkers that allow for earlier decision making (POM/PONV)

**INCREASE EFFICIENCY OF RESEARCH YIELD**
**REDUCE COST: EARLY SIGNALS OF EFFICACY**

Platforms: Transcriptomics, Imaging (MRI), proteomics, metabonomics & select soluble markers, genetics...

Pfizer

PhRMA
Back-ups
Predicting Outcome: Rarely Based on One Parameter

- Contribution of genetic polymorphisms to patient outcomes needs to be considered along WITH other risk factors.

- Factors associated with outcomes:
  - Other exposures
  - Genetic (polymorphism)
  - Acquired
  - Disease, comorbidity

- Factors associated with strength of surrogacy (ICH):
  - Biological plausibility of the relationship
  - Prognostic value of the marker
  - Clinical evidence that effect on surrogate corresponds to effect on clinical outcome

Adapted from “The Value, Qualification and Regulatory Use of Surrogate Endpoints in Drug Development” Clin Pharm Therap 2009 (submitted)
I would potentially take this out as although it might be true it is not really pertinent to the discussion / our messages
mchale_d, 4/5/2007
The First Dimension: Biomarker types

**Target Biomarker:**
measures physical or biological interaction with the molecular target (e.g. PET ligand demonstration of receptor occupancy, measurement of enzyme inhibition, measure of receptor blockade).
Outcome Biomarker:

measures or predicts an outcome (efficacy, safety, differentiation ...) following treatment regardless of the mechanism of action of the compound.

e.g. Viral load or CD4+ cells for AIDS resulting from HIV infection
Mechanism Biomarker:

measures a biological effect presumed to be downstream of the molecular target.

The biomarker may be physiological (e.g. blood flow), biochemical (e.g. change in downstream substrate turnover), behavioural (e.g. reaction time), genetic (e.g. change in gene expression) or proteomic (e.g. change in composition of protein in tissues or biofluids).
Guidance isn't Easy

- Qualification is subjective and complicated
- Many stakeholders need to be satisfied for biomarkers to be considered qualified but they have different value systems
  - scientists perceive principally the understanding of the science
    - can we explain the relationship between the biomarker and the disease?
  - regulators perceive principally risks about failing to protect the public
    - can we detect new risks with new biomarkers?
    - what would happen if a biomarker of benefit was wrong?
  - industry perceives principally the benefit to the patient and to shareholders
    - can we detect new benefits with new biomarkers?
    - can we get drugs on the market earlier by using biomarkers?
  - payors perceive principally the cost
    - if this becomes part of medical practice who will pay and is it worth it?
- How can all these stakeholders be satisfied?
  - accumulate unspecified evidence to over time and multiple replications?
  - develop guidance that efficiently modulates the evidentiary requirements?
Pfizer supports the development of industry-wide standards for implementation in clinical trials that enhance the precision of acquisition of biomarker information or samples, the methods of processing and analyzing signals, and the transfer, archiving and management of data.

- Improve conduct of clinical trials
- Improve regulatory review of data