
Qualification and Use of Biomarkers in Drug Development: Existing Frameworks

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*Institute of Medicine Workshop on Biomarker Qualification
6 April 2009*



Biopharma Perspective on Biomarker Development

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



PhRMA Biomarkers Working Group

Recent Activities:

- u Pharma Company representatives met to discuss concept/context of Biomarker Qualification (April – October 2007)
- u Workshop co-sponsored with FDA to discuss concepts (July 2007)
 - § Case studies presented and discussed
 - § Alignment of FDA and WG thinking
- o **Manuscript to capture Workshop concepts (August-Sept 2007)**
 - § “A prototypical process for creating evidentiary standards for biomarkers and diagnostics” Clin Pharm Therap 83, 2 Feb 2008
- o **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)

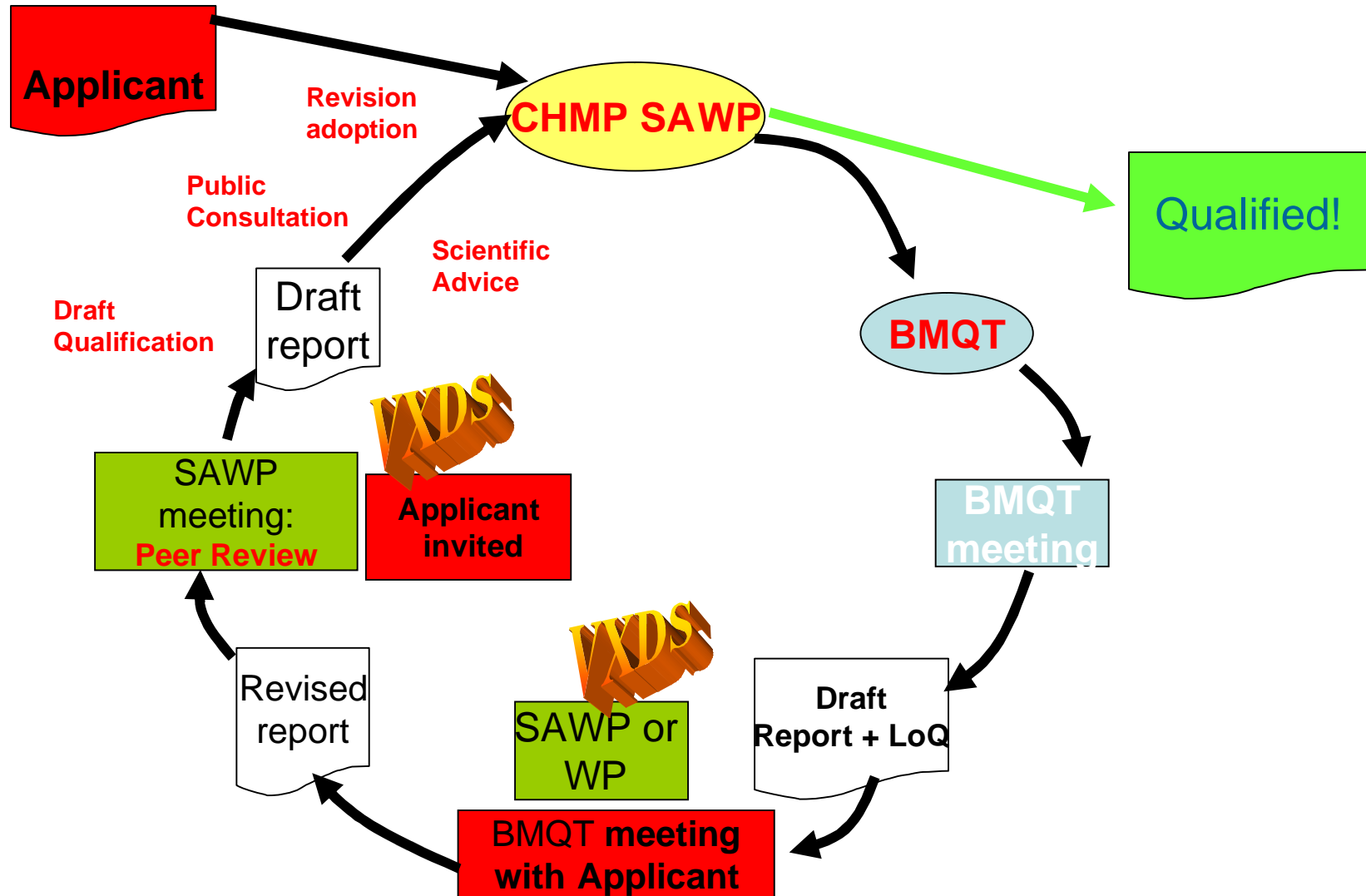


Examples: Global Biomarker Policy Activity

- u **PDUFA IV “Expediting Drug Development” Objectives**
 - o “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”
- u **EMA Draft Guidance “Biomarker Qualification: Guidance to Applicants”**
 - o issued April 2008, comments thru June 2008, CHMP final 22 Jan 2009
- u **Critical Path Institute/Predictive Safety Testing Consortium**
 - o preclinical nephrotox biomarkers FDA endorsed qualification (April 2008)
- u **EC Innovative Medicines Initiative: Translational Biomarkers**
 - o focus on organ toxicity markers and disease mapping markers
- u **ICH E16 Proposal and Discussion June 2008 - ongoing**
 - o Harmonize genomic biomarker data submission and content across regions
- u **Kennedy-Hutchinson “21st Century Cancer ALERT Act”**
 - o 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

- u **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

- u **Sunset or Re-charter when objectives achieved**

- u **Out of Scope:**
 - § technical aspects of biomarker validation & qualification
 - § “platform” specific aspects of validation & qualification



Sharing Biomarker Information

- u 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.
- u The Biopharma Industry recognizes Critical Path and Innovative Medicines Initiative as important developments and is active in supporting efforts to ensure their success
- u Active examples of industry-academic-govt consortia:
 - o Biomarker Consortium http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml
 - o GAIN http://www.fnih.org/GAIN2/home_new.shtml
 - o Predictive Safety Testing Consortium <http://www.c-path.org/PredictiveSafetyTestingConsortium/tabid/219/Default.aspx>



Major Public-Private Partnerships

Grand Challenges in Global Health Partner: Bill & Melinda Gates Foundation	\$200M
Collaboration for AIDS Vaccine Discovery (CAVD) Partners: VRC/NIAID, Bill & Melinda Gates Foundation	\$33M
Alzheimer's Disease Neuroimaging Initiative (ADNI) Partners: NIA & 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	\$27M
Genetic Association Information Network (GAIN) Partners: NHGRI, NLM & Pfizer, Affymetrix, Broad Institute, Abbott Laboratories	\$26M
Observational Medical Outcomes Partnership Partners: FDA, sixteen biopharmaceutical companies	\$21M
Osteoarthritis Initiative (OAI) Partners: NIAMS & Pfizer, Novartis, Merck, GlaxoSmithKline	\$18.5M
Avon-NCI Progress for Patients Award Program Partners: NIAMS & Pfizer, Novartis, Merck, GlaxoSmithKline	\$12M
The Biomarkers Consortium Partners: NIH, FDA, CMS, PhRMA, BIO, pharma/biotech companies, non-profits	\$11.3M*



Biomarkers Consortium Contributing Members (60)

For-Profit Companies (27)

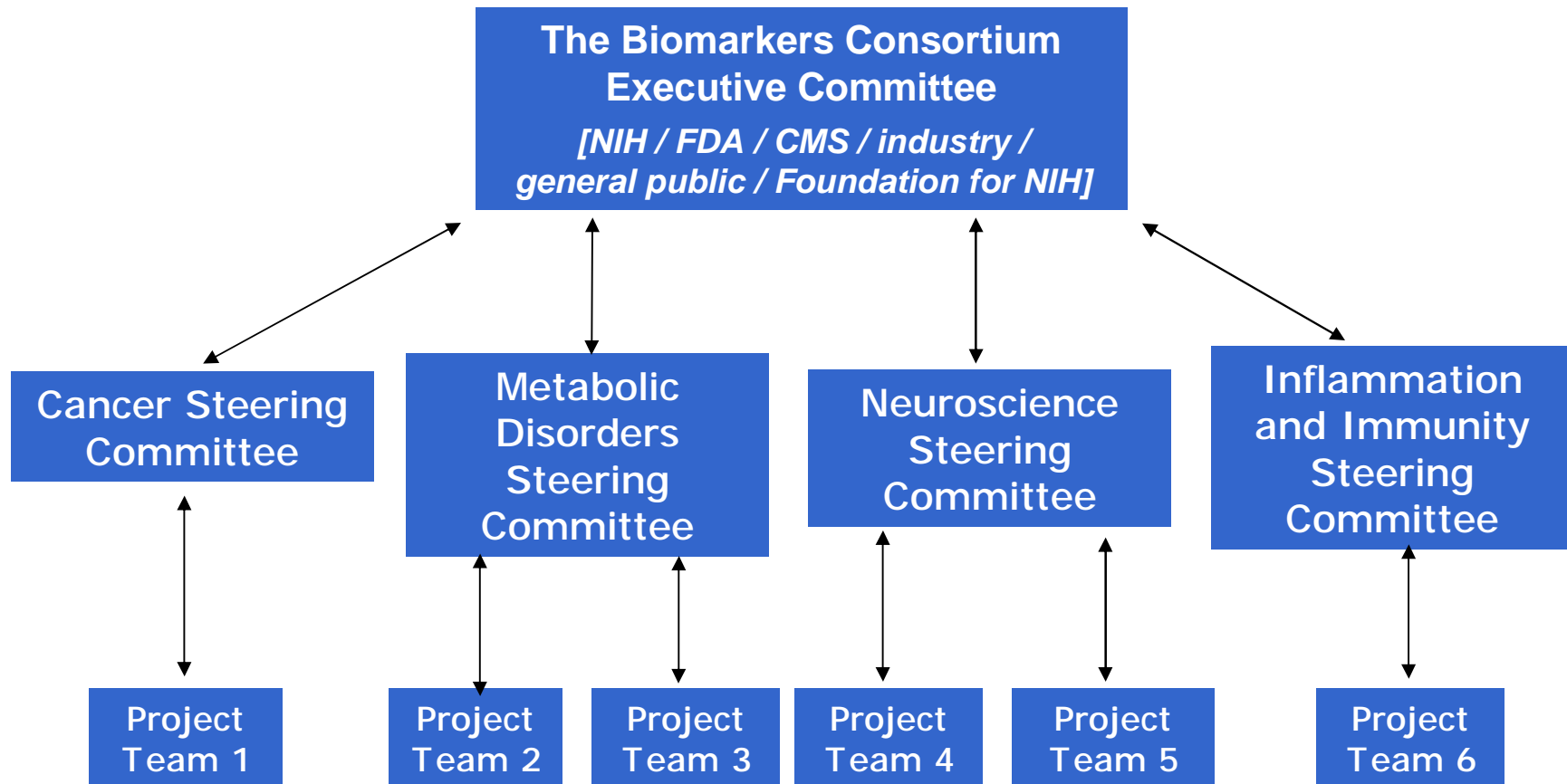
Abbott Laboratories
 Althea Technologies
 AstraZeneca
 Avalon Pharmaceuticals
 BG Medicine
 Boehringer-Ingelheim Pharmaceuticals
 Bristol-Myers Squibb
 Digilab Biovision GmbH
 EMD Serono
 Genstruct
 GlaxoSmithKline
 GVK Biosciences
 InfraReDx
 Ingenuity Systems
 Johnson & Johnson
 Eli Lilly and Company
 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



Definitions - Biomarkers and Surrogate Endpoints

u **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"*

u **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

u **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.

Lee, JW, Devanarayan, V, Barrett, YC, Weiner, R, Allinson, J, Fountain, S et al., (2006) Fit-for-Purpose Method Development and Validation for Successful Biomarker Development *Pharmaceutical Development* **23**, 2, 312-328.



Biomarker Qualification: proposed definition

u **Qualification**

- o 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

Wagner JA, Williams SA, Webster CJ. (2007) Biomarkers and Surrogate End Points for Fit-for-Purpose Development and Regulatory Evaluation of New Drugs. *Clinical Pharmacology & Therapeutics* **81**, 104–107



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.

Biomarker Types (eg):

- Target
- Mechanism
- Functional outcome
- Surrogate outcome
- Safety

Linkage to Outcome:

Low – Medium - High



Biomarker Linkage to Outcome: Triage?

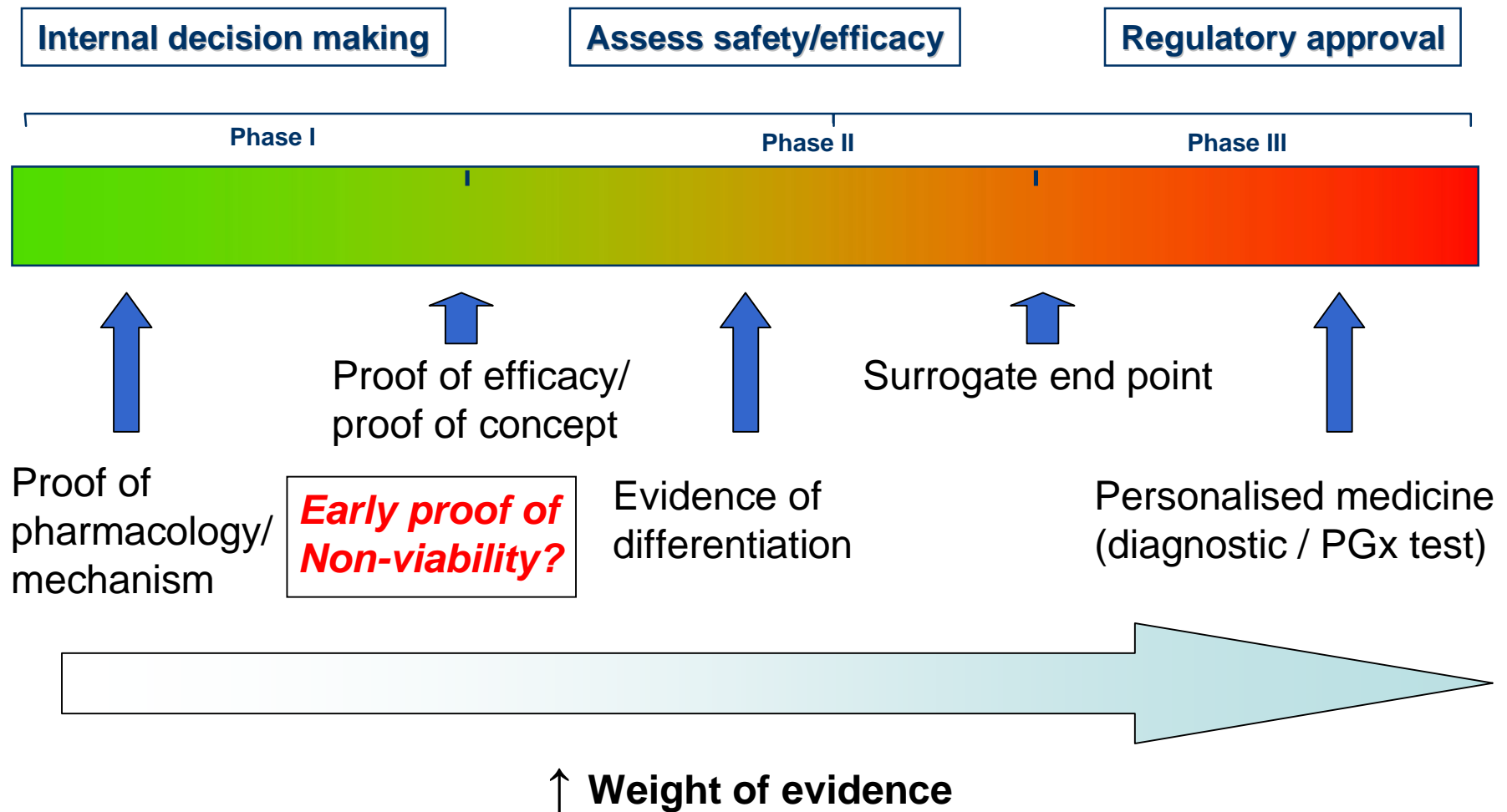
LOW – there is no consistent information on the linkage of biomarker change to efficacy or safety in humans. Linkage to outcomes in animal models may exist. Biological relevance unknown or not clear.

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



Stages of Biomarker Qualification

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

Adapted from: Wagner JA, Williams SA, Webster CJ. Biomarkers and Surrogate End Points for Fit-for-Purpose Development and Regulatory Evaluation of New Drugs. *Clinical Pharmacology & Therapeutics* (2007) **81**, 104–107



Biomarker Qualification Discussion Points

PhRMA Biomarkers Working Group:

- u 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:

- o Consensus from regulators on performance standards for qualification of novel biomarkers
- o Involvement of biomarker technical experts in product review committees
- o Creation of advisory committees outside individual drug development programs for the specific purpose of considering biomarker acceptance
- o Development of a “biomarker label” that specifies accepted uses for specific purposes
- o 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.)

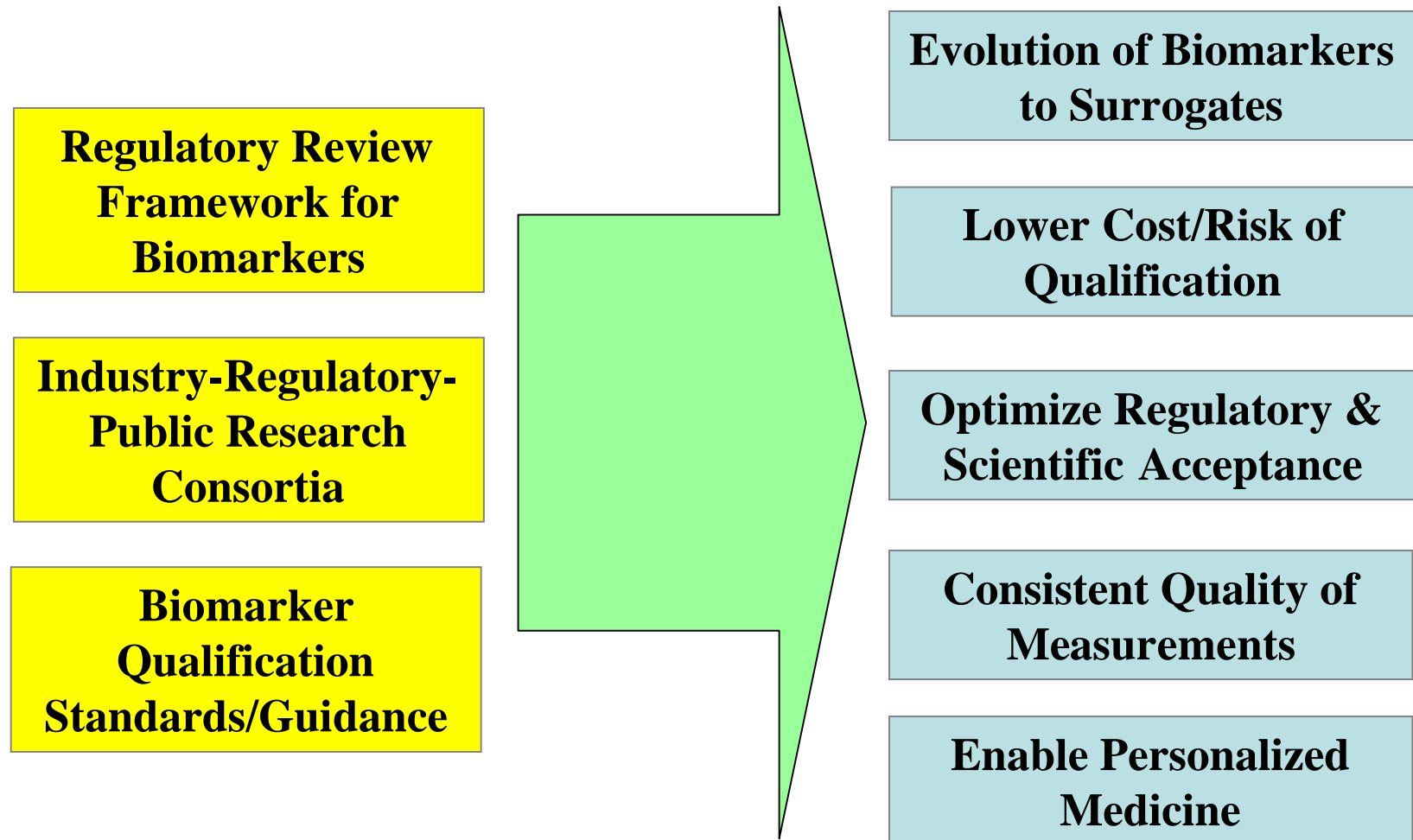
Fit for Purpose Biomarker Evidentiary Standards: Mechanism Biomarker

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

*From: Altar, CA, Amakye, D, Bounos, D, Bloom, J, Clack, G, Dean, R, Devanarayan, V, Fu, Furlong, Hinman, L, Girman, C, Lathia, C, Lesko, L, Madani, S, Mayne, J, Meyer, J, Raunig, D, Sager, P, Williams, SA, Wong, P and Zerba, K (2008) A Prototypical Process for Creating Evidentiary Standards for Biomarkers and Diagnostics *Clin Pharm & Therap* **83**, 2, 368-371

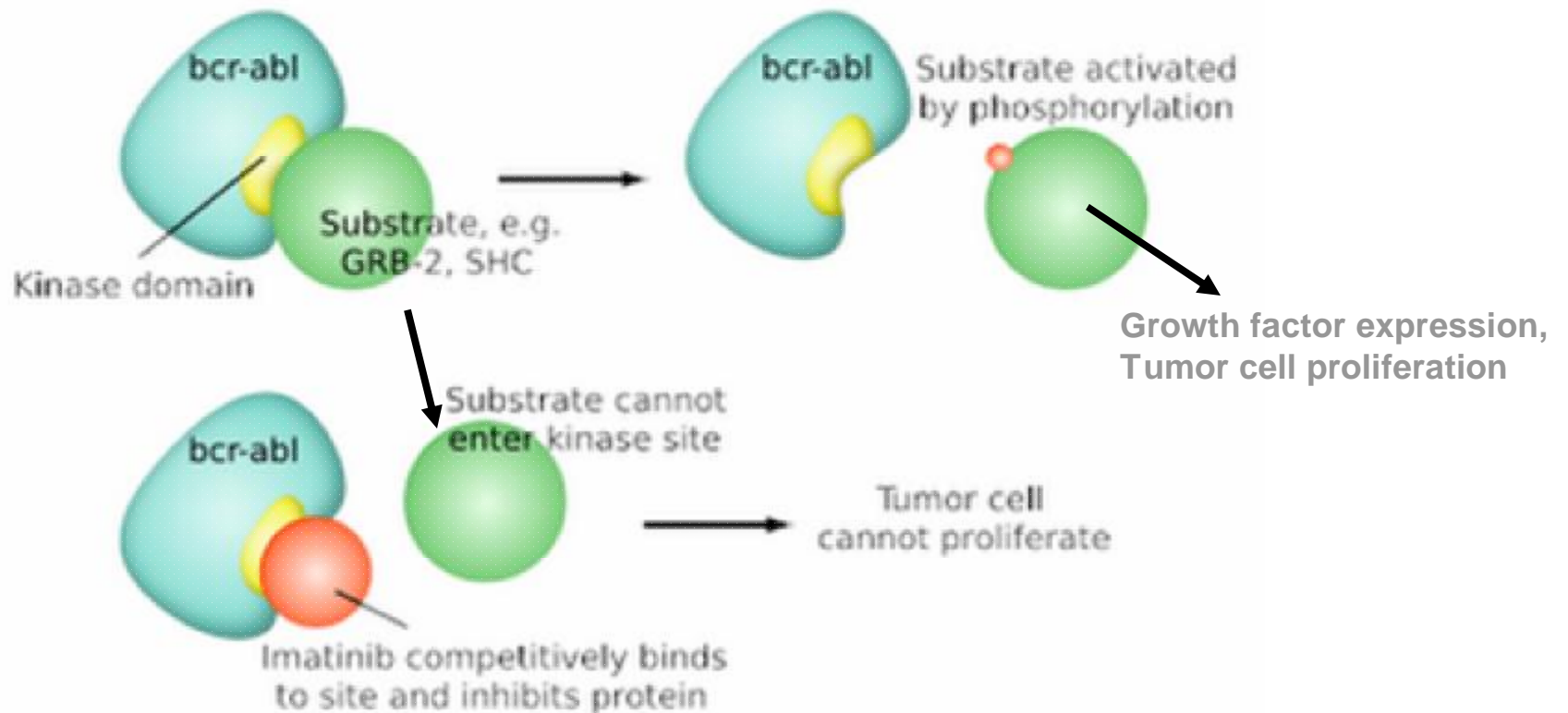


Combined Solutions



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)

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

“Gleevec has converted a once fatal disease into a chronic illness”



Biomarker predicts response & outcome

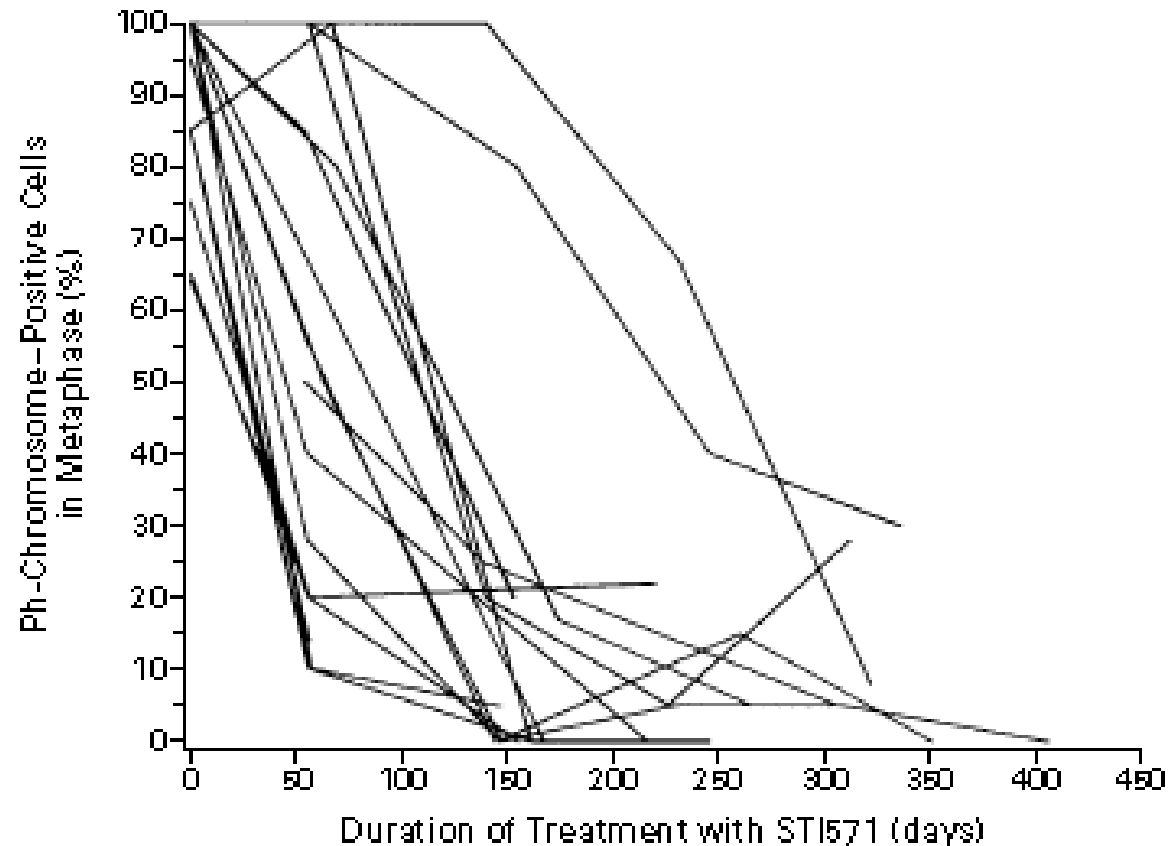


Figure 2. Patients with a Major Cytogenetic Response.

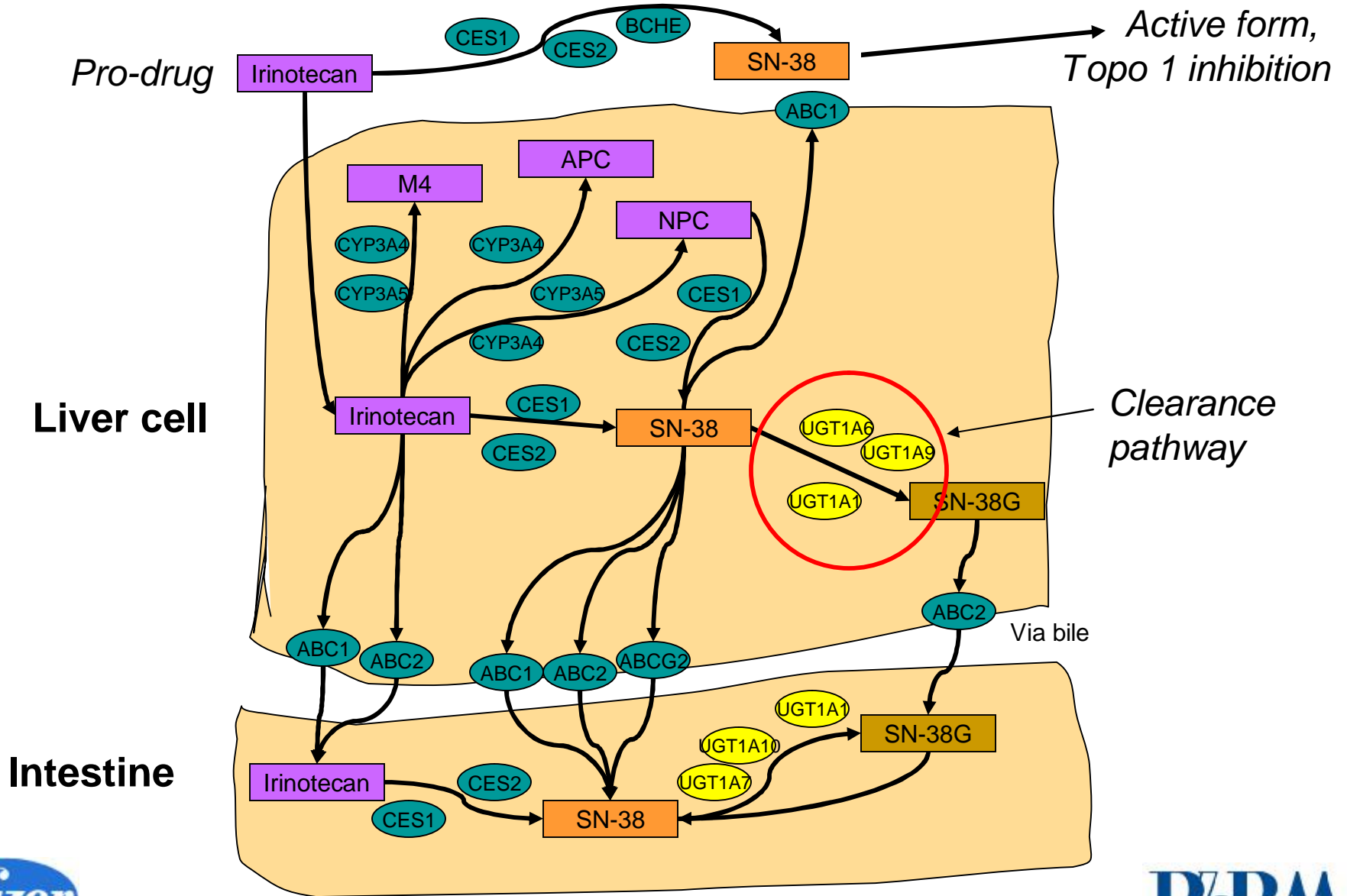
The percentage of cells in metaphase positive for the Ph chromosome (in bone marrow) and the number of days that the patients received ST1571 are shown. Each line represents the cytogenetic response for an individual patient.



Druker et al., N Engl J Med, 344, No. 14, 2001



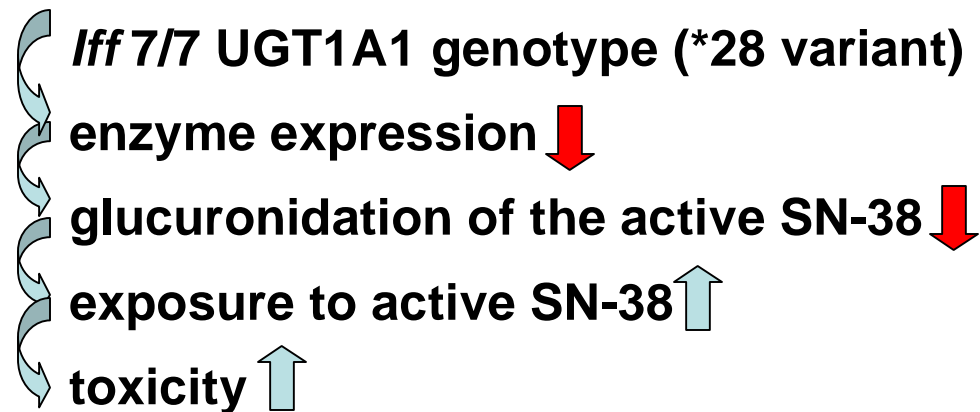
Example: Irinotecan (Camptosar)



Pharmacogenetic Hypothesis

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

The cascade:



Published Data on UGT1A1 & Grade 4 Neutropenia

Unadjusted Odds Ratio

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

^a Gr 3 or 4 diarrhea or neutropenia

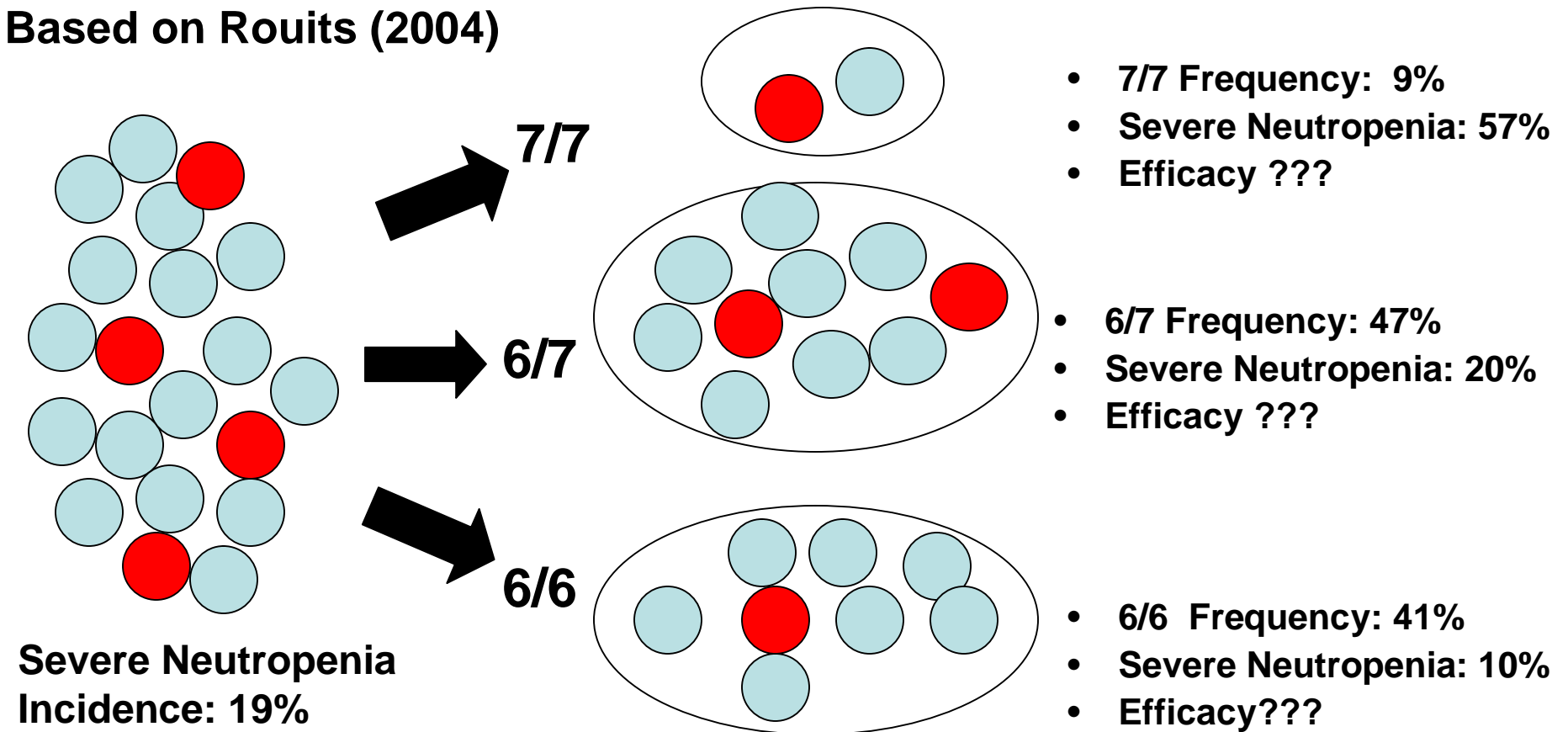
^b Gr 4 values from personal communication. Published values are 3+.

^c Gr 4 leukopenia and/or Gr 3+ diarrhea.



Risk of G4 Neutropenia for UGT1A1*28 Genotypes

Based on Rouits (2004)



Is this sufficient evidence to drive medical practice?

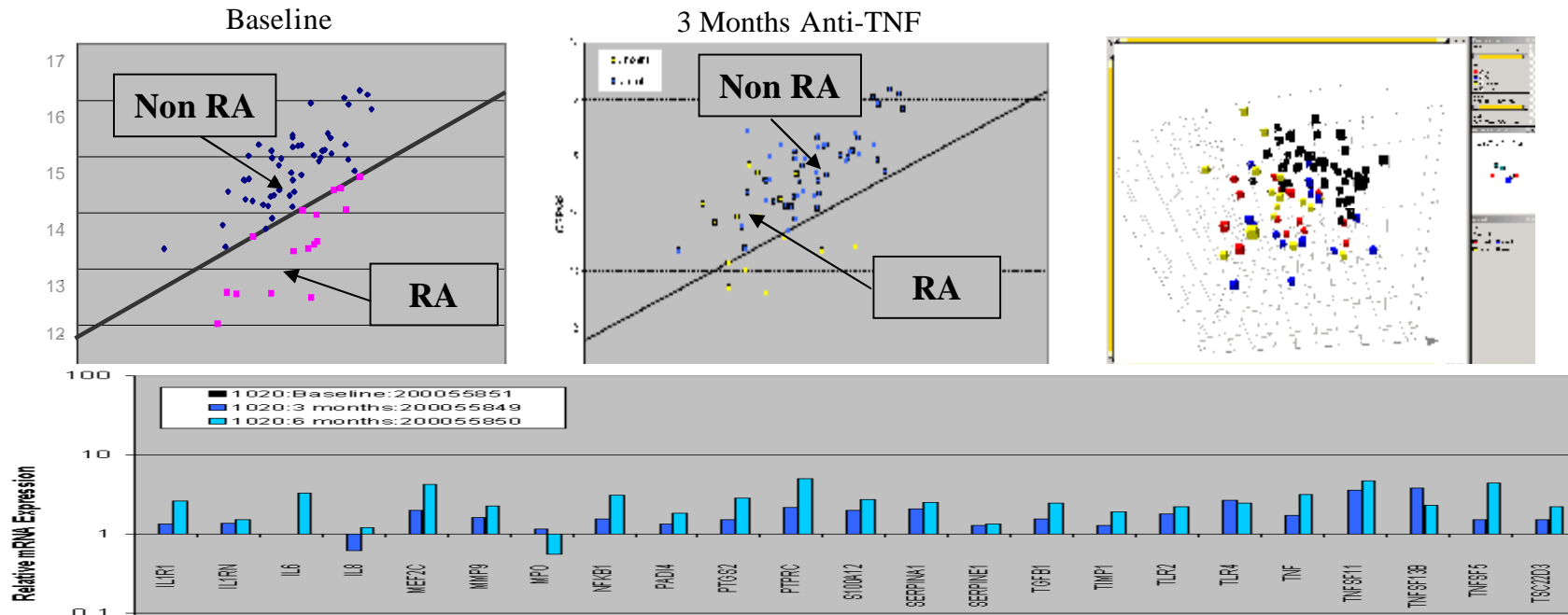


Camptosar /UGT1A1 Summary

- u Evidence of association insufficient to provide a robust predictor of patient outcome or benefit/risk
 - o 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
- u 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)
 - o Innocenti (n=50) – 50%; N9741 (n=497) – 18%; Aviano (n=250) – 5.3%
- u UGT1A1 “biomarker” not qualified for purpose of determining dose or dose adjustment – may be ‘plausible’ but not evidence based without prospective studies
 - o Unqualified marker initially in label for “safety”, excluding some patients
 - o Label later modified to note risk but not prescribe dosing practice



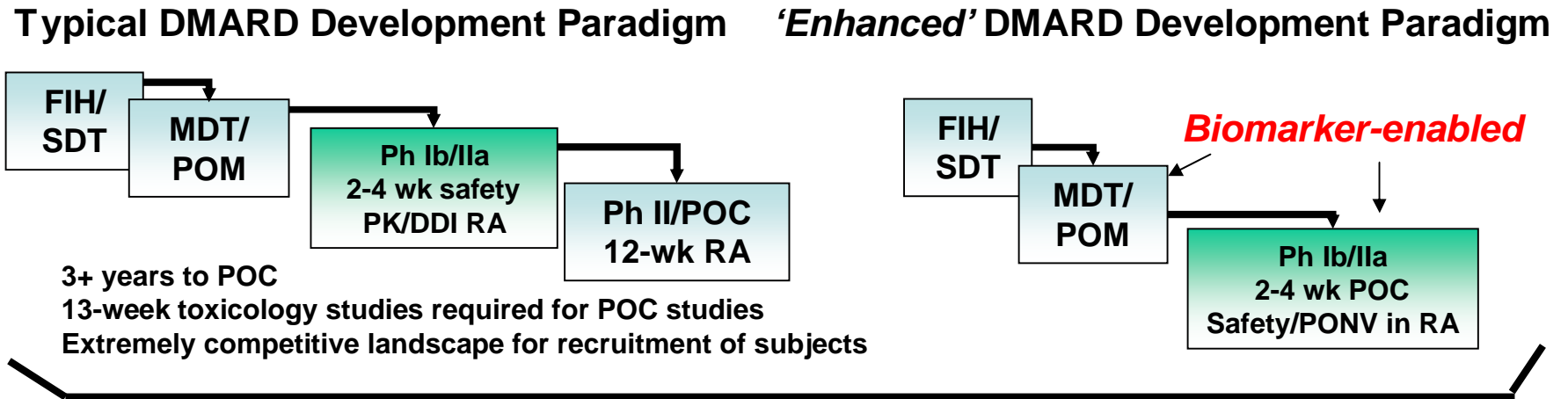
Exploration – Gene Expression in Rheumatoid Arthritis



Expression of Different Genes at Baseline, 3 and 6 months of Anti-TNF therapy in Circulating Blood Neutrophils

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

Applying Genomic Biomarkers to RA Development



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...*



Back-ups



Predicting Outcome: Rarely Based on One Parameter

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

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

- u 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)



Slide 32

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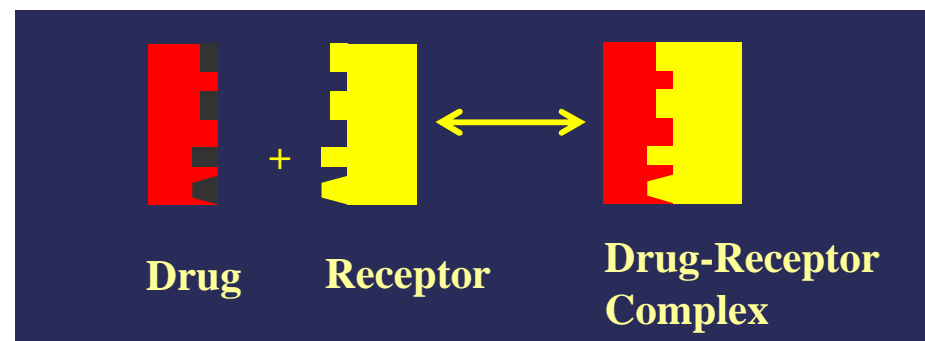
I would potentially take this out as although it might be true it is not really pertinent to the discussion / our messages

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).



The First Dimension: Biomarker types (con't)

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



The First Dimension: Biomarker types (con't)

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

- u Qualification is subjective and complicated
- u Many stakeholders need to be satisfied for biomarkers to be considered qualified but they have different value systems
 - o scientists perceive principally the understanding of the science
 - § can we explain the relationship between the biomarker and the disease?
 - o 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?
 - o 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?
 - o payors perceive principally the cost
 - § if this becomes part of medical practice who will pay and is it worth it?
- u How can all these stakeholders be satisfied?
 - o accumulate unspecified evidence to over time and multiple replications?
 - o develop guidance that efficiently modulates the evidentiary requirements?



Development of Technical Standards for Biomarkers

- u 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.
 - o Improve conduct of clinical trials
 - o Improve regulatory review of data

