The Many Faces of Validation

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Disclaimer

The views expressed in this presentation (and all others today) are the personal views of the author, and do not necessarily represent the view of his employer or the IBS-DR

Validation

- Used in many different ways, depending on the context
  - Research
  - Programming: reproducibility, correctness
  - ..
- Focus on Biomarkers…
- And What About the Statistical Methods?

Validation

- Validation in the pharmaceutical and medical device industry is defined as the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results

(http://en.wikipedia.org/wiki/Validation_(drug_manufacture), accessed: 04.10.2010, 10:00am)

FDA Definition

- *"Validation - Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."*

(FDA Guideline on General Principles of Process Validation, May 1987 – Definitions)

Finding an Answer to a Question

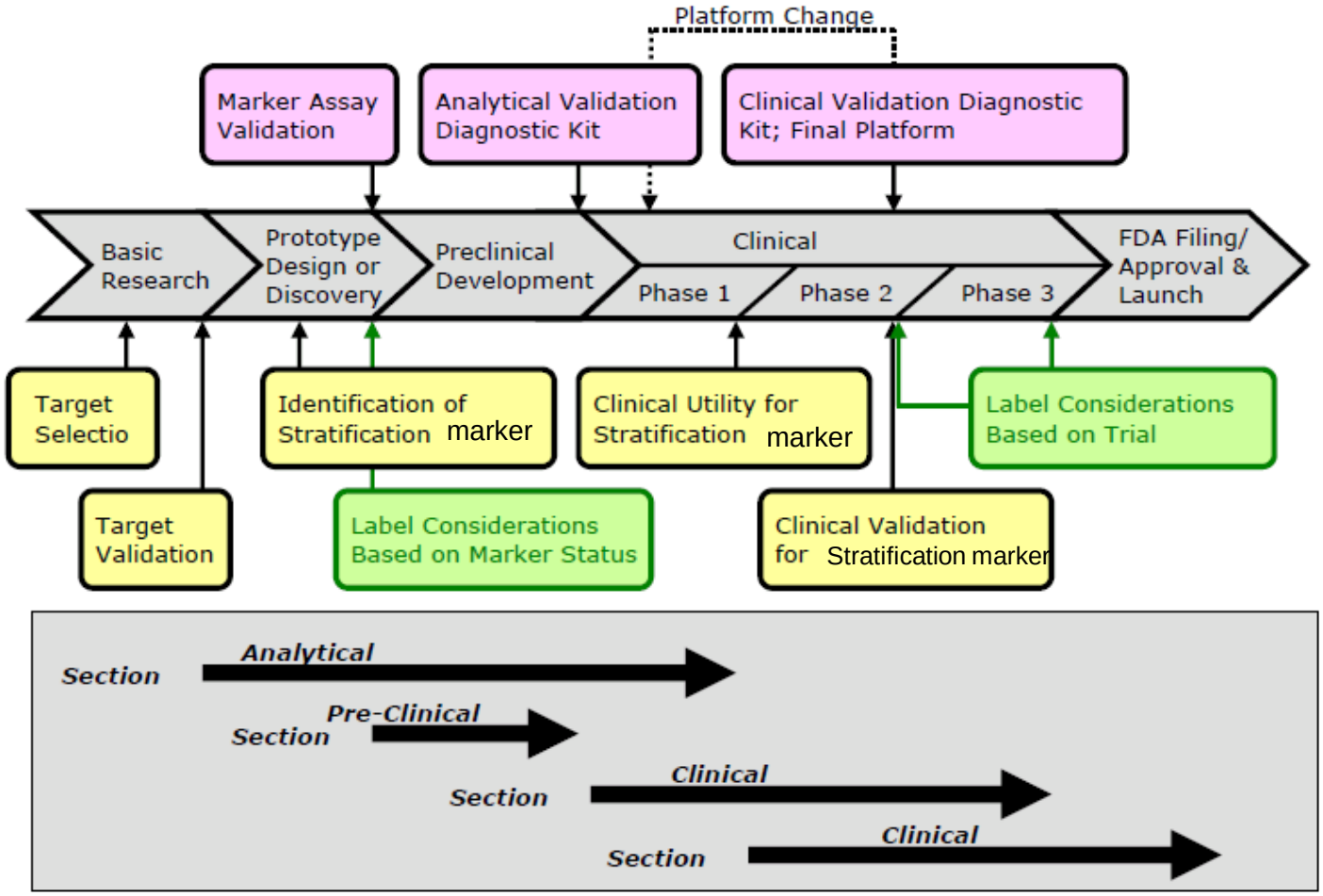
versus

Finding a Question to an Answer

The Use of “Biomarkers”

- Need for targeted medical approaches
  - Prognostic markers
  - Predictive markers
- Need for speed
  - Surrogate markers / surrogate endpoints
- Replacement of animal studies?
  - Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM)
- Paradigm change?

The “process”

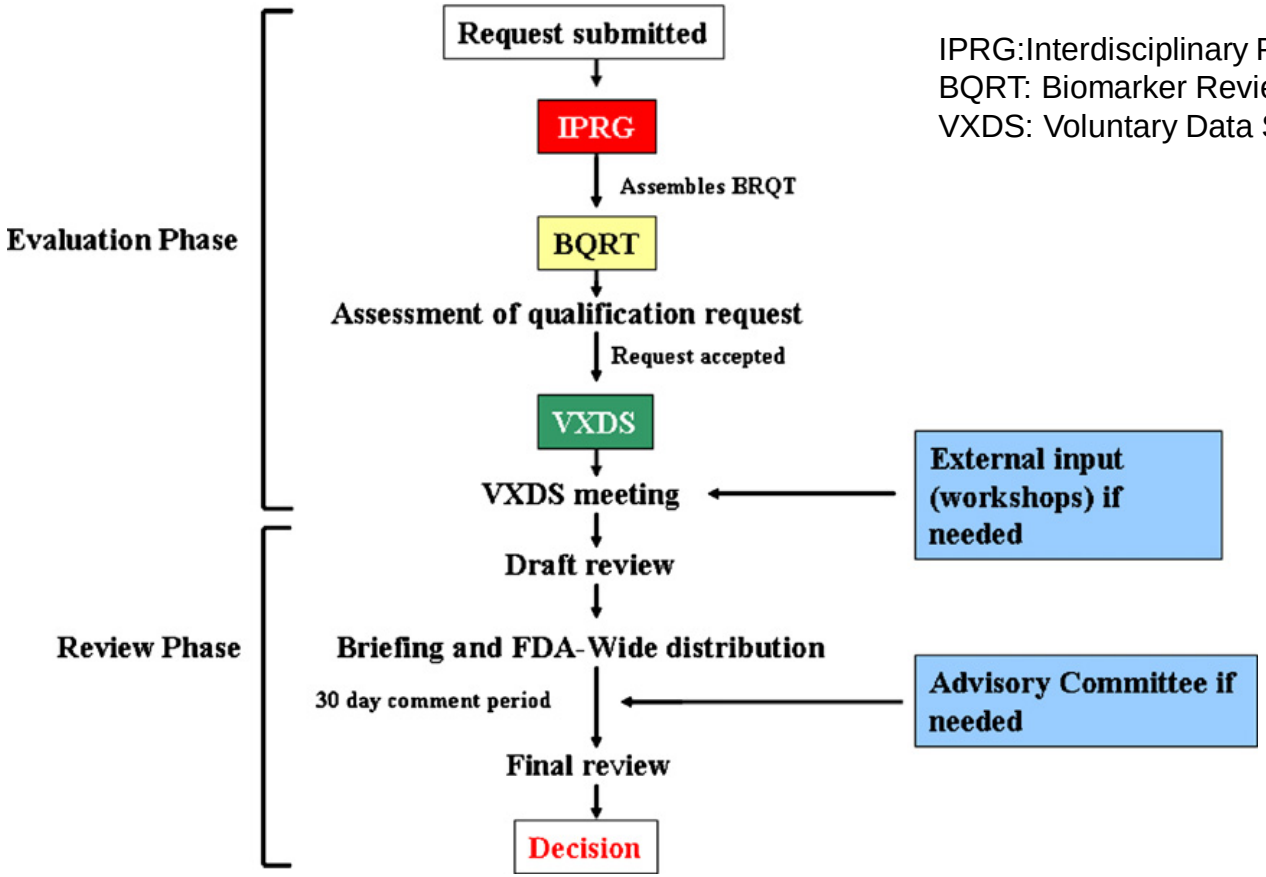


Drug-Diagnostic Co-Development Concept Paper, Draft, FDA, April 2005

Translational BM

- Prerequisite:
  - Same entity in animal and man
  - Consistent functionality
- Validation would require loop back into research

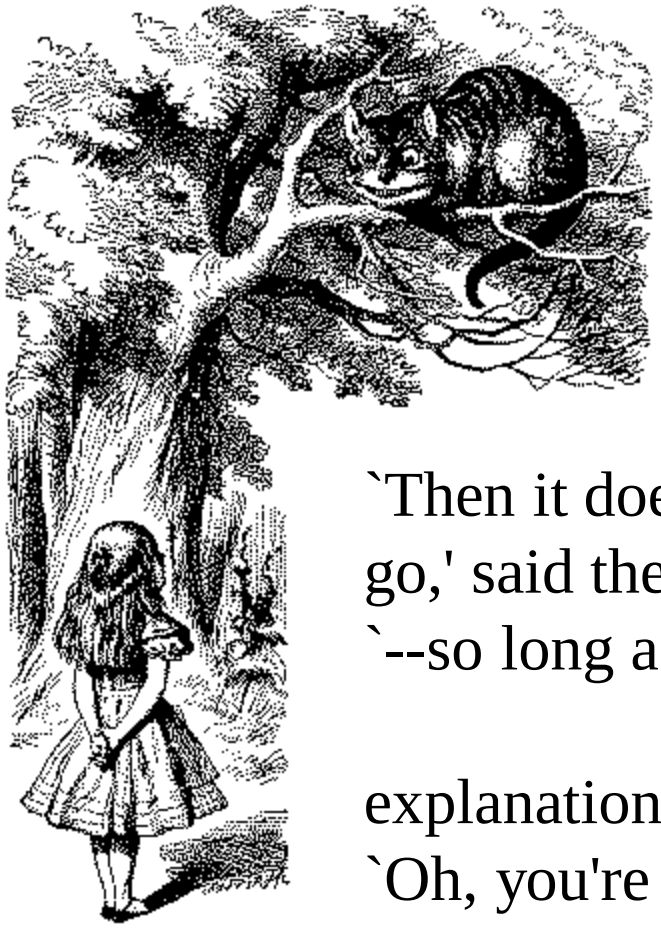
Biomarker Qualification Pilot Process



IPRG:Interdisciplinary Pharmacogenomic Review Group
BQRT: Biomarker Review Qualification Team
VXDS: Voluntary Data Submission

From: Goodsaid, F, Frueh, F, Mattes, M (2008). Strategic paths for biomarker qualification. Toxicology 245: 219-223.

First Steps…



`Would you tell me, please, which way I ought to go from here?'
`That depends a good deal on where you want to get to,' said the Cat.
`I don't much care where--' said Alice.
`Then it doesn't matter which way you go,' said the Cat.
`--so long as I get *somewhere*,' Alice added as an explanation.
`Oh, you're sure to do that,' said the Cat, `if you only walk long enough.'

I think I saw this idea first at a presentation from Stephen Senn, sometime, somewhere ….

Validating a Biomarker

- "Confirmation by robust statistical methods that a candidate prognostic biomarker, predictive biomarkers or surrogate end point fulfills a set of conditions that are necessary and sufficient for its use in the clinic"

Buyse, M. *et al. Nat. Rev. Clin. Oncol*. advance online publication 6 April 2010; Biomarkers and surrogate end points – the challenge of statistical validation. doi:10.1038/nrclinonc.2010.43

predefined

Validating a Biomarker - Revisited

- Validation of the assay
  - Analytical validation
- Clinical test validation
  - Clinical test validation / clinical test utility
  - Validation of the model
  - Cutpoints
  - Prevalence?

Validating the Assay

- Know what you are measuring
- Focus on laboratory component
- Assay characteristics
  - Sensitivity / Specificity / ROCs
  - Repeatability / Reproducibility
  - …

Clinical Test Validation / Clinical Utility

- Methodology depends on purpose
  - Prognostic
  - Predictive
  - Surrogate

Validating the Biomarker

Table 2 | Examples of prognostic and predictive biomarkers and surrogate end points

Type of biomarker	Uses in management and clinical trials	Identification	Validation	Examples
Prognostic biomarker	Treatment choice, patient selection and stratification	Easy, but often flawed or biased	Frequent, but often inadequate because of regression to the mean or flaws in the initial identification study	Poor performance status, elevated hepatic enzymes, multi-site metastases in advanced colorectal cancer.
Predictive biomarker	Treatment choice, patient selection and stratification	Difficult, requires randomized trial	Uncommon, requires large randomized trial	*KRAS* mutation predictive of lack of activity of cetuximab and panitumumab in colon cancer.[18,19] Hormone receptor status predictive of effect of tamoxifen and aromatase inhibitors in breast cancer.[79] HER2/*neu* amplification predictive of effect of trastuzumab and lapatinib in breast cancer.[11–15] *EGFR* mutations predictive of effect of erlotinib and gefitinib in non-small-cell lung cancer.[80]
Surrogate end point	Treatment choice, treatment evaluation	Very difficult, requires meta-analysis or large randomized trial	Rare, requires meta-analysis or large randomized trial	Progression-free survival as a surrogate for overall survival for fluoropyrimidine-based regimens in treating colon cancer.[66] Hematologic complete remission for time to disease progression in patients with leukemias.[46,47]

Buyse, M. *et al. Nat. Rev. Clin. Oncol*. advance online publication 6 April 2010; Biomarkers and surrogate end points – the challenge of statistical validation. doi:10.1038/nrclinonc.2010.43

Clinical Test Validation

- “Clinical test validation of a new diagnostic for use in selecting drug therapy or avoiding drug therapy should be characterized by studying the test in relation to the intended clinical outcome in patient subgroups with and without the analyte of interest. “
- “Endpoints used in a clinical trial to evaluate treatment efficacy or safety should be the same endpoints used to indicate the clinical utility of a tested biomarker and should provide information on the clinical impact of an analytical test result.”

Drug-Diagnostic Co-Development Concept Paper, Draft, FDA, April 2005

Clinical Test Utility

- “A definitive clinical study for a drug used in conjunction with a predictive biomarker would be one that allows for assessment of a drug’s safety and efficacy (i.e., risk/benefit), as well as for verification of the clinical utility of the biomarker in guiding the drug’s use including appropriate patient selection. “
- Use results of analytical & feasibility studies

Drug-Diagnostic Co-Development Concept Paper, Draft, FDA, April 2005

Validation Steps…

- "Validation steps in the development of an assay for a pharmacogenomic biomarker:"
  - Assay performance evaluation:
    - Validation of analytical performance (e.g. detection of the biomarker).
    - Validation of in vivo clinical performance as relevant for context and intended uses (i.e. sensitivity and specificity in detecting clinically relevant response or status, appropriate cut-off level for ROC interpretation etc.).
    - Further plans in post market surveillance to confirm clinical utility

Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development – Draft. EMA 24 June 2010

Validating a Prognostic Model

- Establishing that the model works satisfactory for patients other than those from whose data the model was derived.

Altman, D, Royston, P (2000). What do we mean by validating a prognostic model? Stat. Med. 19:453-473.

- May still require RCTs to confirm clinical utility
  - For example: therapy selection for “unclear” cases

Validating Predictive Biomarkers

- Enrichment design strategy
  - Aka targeted designs
  - If strong evidence from retrospective analyses that only subgroups benefit / some subgroups do not benefit from treatment
  - Assay reproducibility and accuracy is well established
- “Unselected” design
  - Aka untargeted designs
  - Based on BM x Treatment interaction
  - High(er) number of patients

Validation of Statistical Methods

- Validation / Verification
  - Resampling methods?
  - Publications?
  - Acceptance!

And What About the Software?

- Extensive use of R
  - Documentation?
  - Validation / Verification
- And SAS?

Overall Goal of Validation….

"I must have certainty.
Give it to me;
or I will kill you when I next catch you asleep."

George Bernard Shaw, *Back to Methuselah*, Act I, In the Beginning