Biomarkers: Not just another bioanalytical challenge

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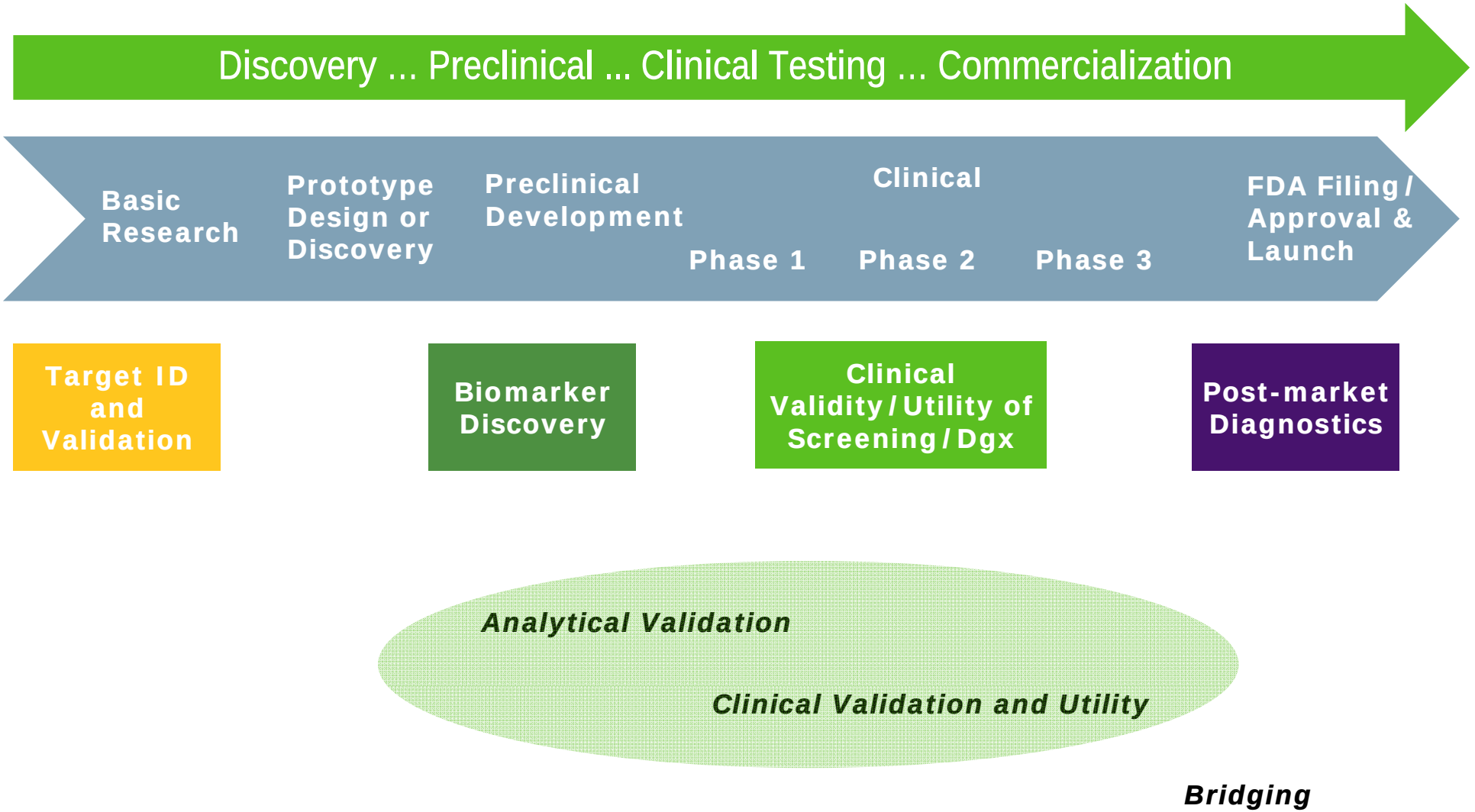
Biomarker Life Cycle



Agenda

1. Intended Use of Data
2. Compliance
3. Analytical Platforms
4. Assay Challenges
5. Industry Challenges

Comparing Intended Use

Bioanalytical

- Dosed
- Quantitative, Qualitative or both
- Determine drug concentration in biological matrix
  - ADME
  - Toxicology
  - Safety & Efficacy
  - Pharmacokinetics
  - Drug-Drug Interactions
- Drug metabolites
- Immunogenicity

Biomarker

- Endogenous analyte response to drug
- Quantitative, Qualitative or both
- Measurement or characterization in a biological matrix related to intended use
  - Up/down-regulated
  - Activity
  - Predictive, diagnostic, prognostic, theragnostic, pharmacodynamic
  - Patient selection or stratification
  - Exposure
  - Safety/efficacy
  - Mechanism of action
  - Specific vs pathway
  - Actual or surrogate endpoint

Use of Biomarker Data

- Biomarkers may have a change as a response to a drug or disease.
- Biomarker response does not have to be a change in concentration. It can be a change in activity or function.
- There may be normal ranges of the biomarker, but the response observed may be an increase or decrease and the % change may be great or very slight.
- The normal range can vary both within patient and between patient.
- How normal range is established is variable.

Use of Biomarker Data

- Patient selection: rapid turnaround time, global implementation
- Safety & medical diagnostic related: rapid turnaround time, global implementation, different compliance regulations
- Method validation/compliance/sample analysis and reporting varies based on use of the data
- May be poor standardization of sample collection, processing or curation

Compliance Comparison

Bioanalytical

- Unregulated
  - Screening/discovery
- Tiered fit-for-purpose
- Regulated
  - FDA
  - EMEA
  - ICH
  - ANVISA
  - BARQA
  - OECD

Biomarker

- Unregulated
  - Biomarker discovery
  - Research
  - Exploratory
- Pharma Regulated
  - FDA, EMEA, ICH, ANVISA, BARQA, OECD
  - CAP & CLIA
- Medical Regulated
  - LDT
  - CLIA
  - Diagnostic/Device

Biomarker Compliance Challenges

- Unregulated
- Pharma Regulated
- Medical Regulated
- Fit for purpose = bad term for biomarkers
- Quality Vs. Compliance
- Qualifications & Validations

Analytical Platform Comparison

Bioanalytical

- Technology
  - LC/MS
  - Ligand Binding
- Method Development
  - Custom developed
  - Proprietary
  - Very rare for commercial kit

Biomarker

- Technology
  - LC/MS
  - Ligand Binding
  - Flow Cytometry
  - Molecular Genomics
  - Imaging
  - Other – activity based
- Method Development
  - Custom developed
  - Proprietary
  - Kit based
  - Hybrid

Assay Challenges Comparison

Bioanalytical

- Pre-analytical Factors
  - Study Design
  - Compliance
- Analytical Factors
  - Compliance
  - Method Development & Validation
- Data Processing & Reporting
  - Study based

Biomarker

- Pre-analytical Factors
  - Study Design
  - Test selections
  - Laboratory selections
  - Geography
  - Compliance
- Analytical Factors
  - Compliance decisions per analyte
  - Method Development & Qualification/Validation
- Data Processing & Reporting
  - Study & sample/patient based

Biomarker Assay Challenges: Study Design

- Range of samples/time point possible for each study
- Shared samples for many biomarkers
- Healthy vs Diseased performance differences
- Potentially different locations, labs, companies, instrumentation, methodology and SOPs
- Sample collection, processing and shipping inconsistencies
- Matrix selection & volumes

Biomarker Assay Challenges: Methodology

- Sample preparation, linearity, precision, selectivity, sensitivity, sample and reagent stability, reagent specificity and availability, parallelism
- Surrogate matrix
- Reagents
  - No COA, heterogenous, source unknown
  - Often no lot to lot continuity
- Trueness
- Within and between study – multiple methods, technologies, matrices possible
- Clinical performance

Industry Structure Comparison

Bioanalytical

- Pharma/Biopharma:
  - Discovery
  - DMPK/Bioanalytical
  - Outsourcing & Procurement
- CRO:
  - Bioanalytical group
    - LC/MS
    - LBA
- University:
  - Research
  - Clinical

Biomarker

- Pharma/Biopharma
- CRO
  - Bioanalytical
  - Central Labs
  - Specialty Labs
- University
- Medical/Clinical Diagnostics
- Companion Diagnostics
- Vendors

Industry Challenges for Biomarkers

Pharma/Biopharma

- Bioanalytical
- Translational Sciences
- Biomarker
- Clinical
- Outsourcing & Procurement

CRO

- Bioanalytical group
  - LC/MS
  - LBA
- Central Lab
  - LC/MS
  - LBA
  - Flow Cytometry
  - Molecular genomics
  - IHC
  - Anatomical Pathology
  - Clinical Chemistry

Industry Challenges for Biomarkers

CRO

- Clinical Diagnostic & Hospital
  - Medical
- University
  - Research
  - Medical
- Specialty Lab
  - Molecular genomics
  - Proteomics
  - Metabolomics
  - Other 'omics

Summary

- Bioanalysis of drugs can be challenging
- Bioanalysis/characterization of biomarkers can be extremely challenging from an analytical, logistical and compliance standpoint
- The challenges between these are often not the same
- The intended use of biomarkers dictates many decisions

Insightful Papers

- Pragmatic issues in biomarker evaluation for targeted therapies in cancer. Armand de Gramont, Sarah Watson, Lee M. Ellis, Jordi Rodón, Josep Tabernero, Aimery de Gramont & Stanley R. Hamilton. Nature Reviews Clinical Oncology 12, 197–212 (2015) doi:10.1038/nrclinonc.2014.202, Published online 25 November 2014.
- Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Christine M. Micheel, Christine M., Committee on Qualifications of Biomarkers and Surrogate Endpoints in Chronic Disease, Institute of Medicine. 06/25/2010.
- Translation of proteomic biomarkers into FDA approved cancer diagnostics: issues and challenges. Anna K Füzéry, Joshua Levin, Maria M Chan and Daniel W Chan. Clinical Proteomics 2013 10:13.
- http://bcn2014.europeanbioanalysisforum.eu/site/ebf_bcn2014/assets/slides/pdf/Marianne_Scheel_Fjording.pdf
- Abdel-Baset Halim (2011). Biomarkers in Drug Development: A Useful Tool but Discrepant Results May Have a Major Impact, Drug Discovery and Development - Present and Future, Dr. Izet Kapetanović (Ed.), ISBN: 978-953-307-615-7, InTech, Available from: http://www.intechopen.com

Insightful Papers

- Lee, J. W., W. Devanarayan, Y. C. Barrett, R. Weiner, J. Allinson, S. Fountain, S. Keller, I. Weinryb, M. Green, L. Duan, J. A. Rogers, R. Millham, P. J. O'Brien, J. Salistad, M. Khan, C. Ray, and J. A. Wagner. 2006. Fit-for-purpose method development and validation for successful biomarker measurement. Pharmaceutical Research 23(2):312–328.
- Evaluation of biomarkers and surrogate endpoints in chronic disease / Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease, Board on Health Care Services, Board on Health Sciences Policy, Food and Nutrition Board, Institute of Medicine ; Christine M. Micheel and John R. Ball, editors. p. ; cm. Includes bibliographical references. ISBN 978-0-309-15129-0 (pbk.) — ISBN 978-0-309-15130-6 (pdf)

Thank you…

Abstract

EBF Abstract: The term biomarker immediately creates confusion when mentioned within the ranks of bioanalytical scientists. This is a result of many inputs – industry perspectives and trends on what biomarkers are and how they are used in discovering, developing, commercializing and administering pharmaceuticals, the specific therapeutic area(s) that the biomarker is used in, and the preferred platform of the organization/department requesting the biomarker vs. the preferred platform of the organization/department being tasked with developing or outsourcing the biomarker. There are also details regarding the analytical matrix type, volume, number and type of sample collections per timepoint, concentration range, number of samples, how the data will be used, compliance decisions, business decisions and technical/scientific decisions.

Abstract

The primary platforms used for biomarker analysis include ligand binding assays, flow cytometry, molecular genomics, LC/MS and immunohistochemistry/imaging technology. The issue that faces many organizations is that these technologies are typically not all placed in a single organization or management structure. Ligand binding and LC/MS are often combined within a bioanalytical organization, but even these can be located in different geographic locations and management. This makes the planning and execution of biomarker strategies challenging. Some organizations have created formal biomarker departments that guide the strategy or even the technological approaches. Others have organized "Biomarker Working Groups" that assist in guiding the organizations biomarker strategy as well as assisting in the biomarker strategy of individual studies. However, there are still many disconnects with resulting inefficiencies that can occur even within or between any organization. For both pharma and CRO's, these are problematic and are further complicated by the Central Lab and Bioanalytical Lab interfaces, their operational structure and the regulatory compliance applied – ie, CAP, CLIA, GCLP, GLP and the ubiquitous fit for purpose.

Abstract

Because the best way to optimize issues is to identify them, this talk will highlight the inefficiencies in the current "business model" surrounding the analysis of biomarkers as well as highlight and discuss the drivers that should be of paramount importance in deciding how to approach biomarker decisions surrounding platform, compliance and general approach to the analysis of biomarkers.