

# “Fit-For-Purpose” and Biospecimen Quality

**Sifting for gold dust in a mine of coal**

# “Fit-For-Purpose”

- Contingent performance in the context of what is needed – Nursing literature – 1978
- 141 peer review reports (24 about nursing)

# “Fit-For-Purpose”

- Appeared in association with the term biomarker in 2006
- Lee et al – “Fit-for-purpose method development and validation for successful biomarker measurement”
- Appears derived from Biomarker Method Validation Workshop – October 2003 (AAPS and CLAS)

# Context of Report

- Concern that the process of biomarker development and validation replete with uncertainty
  - Regulatory implications
  - Scientific requirements
  - Lack of uniform definitions
- Appreciation that differences in traditional drug level studies and studies needed for biomarker research

# Eight Publications

- Differing themes
- Central premise -- differing validation methods and criteria for different uses

# Wagner -- 2007

- Exploration – R & D stage
- Demonstration – proof of concept stage
- Characterization – does it actually work stage and if so how well
- Surrogacy – is it good enough to replace traditional outcomes and provide streamlined studies

# Pepe - 2001

- Preclinical exploratory studies
- Clinical assay and validation
- Retrospective longitudinal
- Retrospective screening
- Disease



# Chau -- 2008

- Target discovery and validation
- Lead discovery and optimization
- Preclinical studies
- Clinical trials

# Lee et al

- Continuous and iterative cycle
  - Pre-validation
  - Exploratory method validation
  - Advanced method validation
  - In-study method validation



# Common Key Elements

- Reagents and reference material
- Target range
- Dynamic range
- Sensitivity (analytical)
- Curve fitting
- Selectivity and specificity

# Common Key Elements

- Dilution linearity
- Precision and accuracy (analytical)
- Relative accuracy/recovery (biological)
- Robustness (reagent and change control)
- Sample handling, collection, processing and storage
- Documentation

# Startling Assessment

- Need all elements at all stages
- Matter of degree of certainty; not a choice to ignore the element
- Matter of opinion what the matter of degree might be

# Sensitivity (analytical)

- Preanalytical and method development – define minimum detectable range and requirements of sensitivity (LOQ)
- Exploratory method validation – estimate sensitivity – consider (LOQ)
- Advanced method validation – establish sensitivity

# Sample Quality Counts

- Head on and head's up
  - “Early, consistent application of predefined sample collection and handling techniques”
  - “Definitive assessment of short-term, freeze/thaw, bench-top, and long-term stability”
  - “A complete set of separate investigations should evaluate the most appropriate conditions for collecting and treating study samples to ensure the sample integrity is maintained”

# Sample Quality Counts

- Prescient – submission July 2005
- “Patient-related factors including diurnal, disease-related, and behavioral effects (i.e., emotional state, posture, food intake, etc.) may necessitate alterations in sampling methods and careful interpretation of biomarker data.”

# Sample Quality Counts

- Definitive
- “Deliberate ‘stressing’ of samples may reveal ... artifacts... and provide vital sample collection tolerance information.”
- **Gold Star**
- Punch line – need to know what to stress

# Specimen Collection

- Not exactly a new issue – first report in literature in 1969 (Russian)
- Mainstream lab requirement with CAP lists in 1970's
- Specimen -- sample collections referenced in relation to quality in tens of thousands of publications

# Preanalytical Laboratory Error

- Major factor – 46 to 68% of cases of error
- Errors noted in chemistry and molecular diagnostic labs -- mundane
  - Labeling error
  - Wrong container
  - Clotted sample
  - Hemolysis

# Preanalytical Laboratory Error

- Recent reports on systemic root causes
  - Non laboratory collection settings
  - High rate of staff collecting without looking for rules of the game (40%)
  - Pre-labeling (12%)

# Elaborate Risk Management Programs

- Process analysis
- Reassessment and rearrangement of quality requirements
- Dissemination of operating guidelines and best-practice recommendations
- Introduction of error tracking systems
- Use of redundancy

# Elephant in the Room

- Ensure control over preanalytical process a prerequisite is to understand the process
- Uncertainty remains
  - What questions to ask
  - How to design studies to address the questions
  - Clash between pragmatism and purism
  - Strength of the noise in the context of the strength of the signal
  - Underlying biology versus underlying chemistry (technology) being employed

# Inevitable Tide of Resilient Scientists

- Won't take no for an answer
- In cases where there may be degraded or inadequate sample; always someone willing to push the limits and look for analyte retrieval or salvage

# Inevitable Tide of Resilient Scientists

- More markers than data
- More models than markers
- Perhaps just a touch of madness in the race for the gold; when you go fishing it is wise to
  - Know the quality of water you are exploring
  - Use appropriate bait
  - Have a good pole



# In this Maelstrom

- Fit-for-purpose becomes highly relevant
- How good is good enough
  - Understanding underlying biology
  - Understanding confounding factors
  - Understanding interface between technology and these factors
  - Determining if the facts of the case make it “fit”



# Hard Work at Qualifying

- DNA
- RNA
- Proteins
- Metabolites



# Hard Work at Qualifying

- Yield
- Purity
- Freedom from interference
- Stability
- Biological state
- If multivariate (inevitable interplay)

# End Game Not New

- Biomarker that works
- Hierarchy of knowledge – Fryback and Thornbury in 1991
- Imaging literature -- nobody has done it better

# End Game Not New

- Level 1 – **Technical efficacy**
- Level 2 – Diagnostic accuracy efficacy
- Level 3 – Diagnostic thinking efficacy
- Level 4 – Therapeutic efficacy
- Level 5 – Patient outcome efficacy
- Level 6 – Societal efficacy

# Rules Expanded

- Exquisitely limned in the ACCE Model – used in CDC EGAPP projects
- Analytical validity, Clinical validity, Clinical utility, and associated Ethical, legal and social implications)

# Rules Expanded

- 44 Questions or elements for a full scale evaluation
- At the base are 9 questions on analytical validity
- Underlying these are four central themes
  - Analytical sensitivity – how well signal is detected
  - Analytical specificity – what interferes
  - Quality control – how do you know the procedure is working correctly
  - Assay robustness – how resistant is the assay to changes in **pre-analytic and analytic** variables



# Parochial View from Central Florida

- Whether you subscribe to the Fryback-Thornbury model, the ACCE model, or some other model
- Game of baseball; cannot get to second base if you don't get past first base; cannot get a home run with a foul ball



# Fit-For-Purpose

- **Merits** to a contingent approach;
- Biomarker technology is iterative
- Information on biologic underpinnings is continuously evolving
- Resources (funds, time, specimens) are limited

# Fit-For-Purpose

- **Hazards** to a contingent approach
- Shortcuts up-front in both analytical and clinical validation may be pragmatic; may also be painful because they can increase downstream risks
- Probably not public health risks but risks to reputation, riches, and glory
- Extent they yield fool's gold; does hurt the public

# House of Cards

- Minimum standards for preanalytical and analytical validity are needed up-front to support robust discovery – *not inconsistent with fit-for-purpose*
- Standardization of both preanalytical and analytical methodology and information sharing is needed to accelerate product development in this arena
- Standardization of clinical methodology and information is needed to accelerate product development in this arena.

# The Disquieting Muses - Plath

- Day now, night now, at head, side, feet,  
They stand their vigil in gowns of stone,  
Faces blank as the day I was born,  
Their shadows long in the setting sun  
That never brightens or goes down.  
And this is the kingdom you bore me to,  
Mother, mother. But no frown of mine  
Will betray the company I keep.