REPEATABILITY, REPRODUCIBILITY AND ANALYTIC STANDARDS FOR BIOMARKER DEVELOPMENT

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Disclaimer

This presentation is solely the authors’ own perspective and should not be construed to represent any Food and Drug Administration determination or policy.
UPDATES

• Dr. Chris Leptak, Director Biomarker Qualification Program

• Analytical Validation White Paper

• FDA Guidance Document
ANALYTICAL VALIDATION

• A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. (BEST Resource)

• This process is a validation of the test’s, tool’s, or instrument’s technical performance, but it is not a validation of the item’s clinical usefulness (Clinical Validation). (BEST Resource)
Plan for analytical validation should be described early in the biomarker qualification process.

Acceptable test performance depends on the Context of Use (COU) and risk associated with the biomarker.

Impact of biomarker in decisions for drug clinical trials
CONTEXT OF USE

- COU is a concise description of the biomarker’s specified use in drug development.
- A COU is generally written to be consistent with the following structure:

  [BEST biomarker category] to [drug development use].
“…TKV, measured at baseline, [is] a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient’s estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient’s age and baseline eGFR as an enrichment factor in these trials.”

WHAT IS THE EVIDENCE REQUIRED?

• Answer – it depends on the Context of Use

“this device provides tools for measuring volume” ≠ “this device may be used to measure changes in tumor volume greater than 25 mm³ from CT images in patients with lung cancer”
FIT FOR PURPOSE

• Fit-for-purpose is a conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use.

• Biomarker method is *deemed acceptable* if the assay is capable of discriminating changes that are statistically significant from the intra- and inter-subject variation associated with the biomarker.

• Performance characteristics are *deemed acceptable* if:
  • Assay can distinguish biomarker changes that are outside of expected normal variability.
PRE-ANALYTICAL CONSIDERATIONS

- Pre-analytical factors refer to procedures that occur prior to sample analysis.
- Refers to factors such as collection, processing, transportation, and storage.
• Calibration of the measurement method and maintaining system function in accordance with a specification or standard.
COMMON ANALYTICAL PARAMETERS

• Accuracy
• Measurement Method Range
• Precision
• Repeatability
• Reproducibility
ACCURACY

• Accuracy is the closeness of agreement between the result of a measurement and the true value of the measure.

• Need a comparator (current standard, ground truth, etc.)
ANALYTICAL MEASUREMENT RANGE (LLOQ, ULOQ)

• The Analytical Measurement Range (AMR) is the range of values that a method can directly measure on the measurand.

• AMR validation is the process of confirming that the system will correctly recover the concentration or activity of the measurand over the AMR.

• Requires measuring Lower and Upper Limits of Quantification (LLOQ and ULOQ, respectively).
PRECISION

• Closeness of agreement between independent test results.
• Can be expressed using Standard deviation or coefficient of Variation
• Represent the scatter of data not accuracy of reported results.
REPEATABILITY

• Precision determined under unchanged conditions.
• Measured using the same method, test material, and measurement equipment
• Same lab/facility
• Same operator
• Within-series, within run, or intra-assay
REPRODUCIBILITY

- Precision determined under changed conditions
- Measured using same method and test material
- Different lab/facility
- Different operators
- Different equipment
DIFFERENT TYPES OF BIOMARKERS HAVE SPECIFIC ANALYTICAL PARAMETERS

- Assays
- Imaging
ANALYTICAL PARAMETERS FOR ASSAYS

• Selectivity
• Parallelism
• Stability
SELECTIVITY/INTERFERENCE

• Selectivity is the ability of the assay to accurately measure the analyte unequivocally in the presence of interferences or structurally unrelated components that may be expected to be present in the intended matrix.

• Samples from multiple individuals of normal and target patient populations should be tested for the endogenous value of the target biomarker in each individual sample.
PARALLELISM

• Parallelism is the extent to which the analyte concentration relationship between two materials (i.e., calibrator versus unknown specimens) is constant for the examined range of concentrations.

• Enables identification of potential interference factors in the desired matrix.

• Parallelism is the demonstration that the sample dilution response curve is parallel to the standard concentration response curve.

• It is necessary to establish that the interaction of the critical assay reagents with the calibrator material is similar (parallel) to their interaction with the biomarker in patient samples.

• Parallelism and/or any assay limitations should be determined in the pre-study validation stage,
STABILITY

• Stability under all conditions can be influenced by time, temperature, humidity, the presence of degrading enzymes, the natural half-life of the biomarker, storage conditions, the matrix, and the container system.

• Stability is commonly measured by comparing stored samples under realistic conditions to a set of samples prepared freshly (time zero/baseline results) from a stock solution of standard at known concentrations in an interference free matrix or samples drawn freshly (time zero/baseline) and sub-aliquoted for stress testing (time, temperature, and storage condition).
ANALYTICAL PARAMETERS FOR IMAGING BIOMARKERS

- Image Sharpness / Resolution
- Field of View
- Depth of Field
- Distortion
- Artifact
The ability to resolve two distinct structures in an image
FIELD OF VIEW

• Observable area that can be seen through a optical device

• Angular field of view (FOVA) of an imaging device is defined as the angle in object space over which objects are viewed or recorded on a film or video sensor.

• Angle through which the device can pick up electromagnetic radiation.

• Horizontal and Vertical field of view can be described using dimensions or angle from the image center.
DEPTH OF FIELD

• The nearest and farthest objects in an image that appear sharp in an image
DISTORTION

• Geometric Distortion is a deviation from the rectilinear projection, a projection in which straight lines in a scene remain straight in their image.
ARTIFACT

- Misrepresentations of tissue structures seen in medical images
PERFORMANCE CONSIDERATIONS

• Some important performance characteristics for measurement method (analytical validation) include:
  • Bias
  • Linearity
  • Precision

• Some important performance characteristics for biomarkers (clinical validation) may include:
  • Sensitivity, specificity, PPV, NPV
  • Receiver operating characteristic (ROC), Agreement, precision, utility
ANALYTICAL FACTORS TO CONSIDER

- FDA Cleared or Approved Test
- Lab Developed Test
- Investigational Use Only
- Research Use Only
ANALYTICAL VALIDATION

• Validation should be provided based on the biomarker, its condition of use and drug development use, and risk.
• Platforms/technologies- depend on the biomarker form (protein, RNA, Imaging, etc.) and on the need (qualitative, quantitative, etc.)
• Analytical validation for the biomarker does not constitute FDA clearance or approval for the measurement method
THANK YOU