Bioanalysis ZONE
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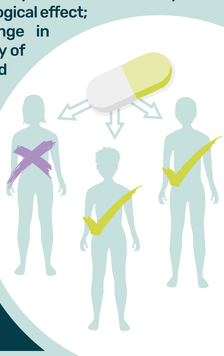
ICON

Biomarker Assays
Bioanalytical meets CLIA

Reliable diagnostic, prognostic, predictive, pharmacodynamic and pharmacokinetic biomarkers are critical to assure correct patient selection, drug dosing and monitoring. Being able to identify the most effective biomarkers and then utilize them to stratify patients and evaluate therapeutic benefit can reduce both drug development time, clinical trial sizes and facilitate more rapid regulatory approvals and time to market. As such, in the early stages of drug development, a drug developer should begin to evaluate biomarkers for potential diagnostic application in parallel with the development of the therapeutic drug itself.

Early research will focus on identifying potential biomarkers based on knowledge of the drug's mechanism of action. The goal is to identify measurable analytes that accurately correlate to an early biological effect; i.e., a measurable change in normal biology. The quality of the biomarker assay need only fulfil the requirements necessary for internal decision-making.

How a biomarker assay is further applied to a drug's development, e.g., as a clinical endpoint (primary, secondary or exploratory) in a clinical protocol, will determine when an assay should evolve from research quality to a clinical diagnostic test or even a Companion Diagnostic (CDx).



1 How do you determine what level of validation is required to measure a biomarker?

Will the biomarker method be used to support a drug application, enrolment or stratification of patients into a trial, evaluate drug safety, or is it being developed as a CDx for drug approval?

In all cases, the biomarker method will be designed as 'fit for purpose' which FDA define as being appropriate for the intended purpose of the study.

FDA

If the assay is being used to support patient response to the therapy (e.g., PK/PD correlation) for inclusion into an NDA or BLA, but not used to direct treatment then analytical validation should be performed following the FDA Bioanalytical Method Validation guidance.

If the assay is being used to support patient selection or stratification (e.g., an interventional clinical trial), a decision to treat (or not) with investigational drug and/or safety endpoints then analytical validation should be performed to CAP/CLIA standards.

If the assay is being used to support an IVD submission as a CDx then analytical validation should be performed to CLSI requirements.

2 Recommendation for assay validation of a biomarker method supporting an exploratory endpoint

Commercial kits can be used following basic validation. Lab developed methods should assess precision, parallelism using incurred samples, selectivity in the presence of drug and drug target, benchtop and freeze/thaw stability. Target acceptance criteria options include % accuracy being within ±2 or 3 times the inter-assay precision.

3 Recommendation for assay validation of a biomarker method supporting a pharmacodynamic endpoint

Follow FDA BMV Guidance including assessment of parallelism and precision using incurred samples, selectivity in the presence of drug and drug target (if different from the PD marker), sensitivity, specificity and stabilities (short-term, freeze/thaw and long-term). The biological matrix for QCs should match study samples, which will require matrix screening to find endogenous levels that cover the dynamic range.

4 Recommendation for assay validation of a biomarker method supporting patient selection, decisions or safety endpoints

Follow College of American Pathologists (CAP) requirements including analytical validation (accuracy, precision, sensitivity, reportable range, and reference range) and clinical validation (reproducibility using authentic clinical specimens).

COLLEGE of AMERICAN PATHOLOGISTS

This infographic has been created as part of a Bioanalysis Zone feature in association with ICON.

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