Uncommonly **BOLD**

# BIOMARKERS IN CLINICAL TRIALS

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# Biomarkers in Clinical Trials

Eurofins Central Laboratory offers exploratory and confirmatory biomarker analysis globally in our 4 CAP-accredited Central Laboratory locations: US, EU, Singapore and China. For modern global clinical trials, utilizing disease-related biomarkers as surrogate endpoints is standard practice. Harmonization and standardization across all laboratory locations is critical for the validity of biomarker utilization. Commercial clinical analyzers and their associated testing kits find great utility in conducting such analyses, and verification of manufacturer specifications is often sufficient for the use in clinical [CAP/CLIA] laboratories.

Biomarker data that is used for decision making and for regulatory purposes, requires advanced method validation beyond CAP/CLIA verification. Eurofins Central Laboratory is uniquely positioned with our Biomarker Center of Excellence by uniting GLP and GCP in one synergetic approach. We are one-of-a-kind in offering advanced validation for biomarker assays on clinical analyzers. Our hybrid system allows us to combine best of both worlds when utilizing aboratory biomarkers to prove safety and efficacy, support go/no-go decisions, stratify patients, develop companion diagnostics and to support the submission of data sets to regulatory agencies worldwide.

Supported by an industry leading Scientific Team, biomarker assays are developed and fit-for-purpose validated to meet the specific requirements of your Clinical Trial Program. As our Biomarker Services are fully integrated in our Central Laboratory, we offer a seamless transition to a high volume production testing environment under one roof.

## Achieve the best possible outcome of scientific excellence

With Eurofins Central Laboratory acting as the hub, we provide our clients access to over 100+ specialized laboratories in the Eurofins BioPharma Solutions network. This model offers an exhaustive range of state-of-the-art technology platforms to support all laboratory biomarker testing requirements spanning protein, genomic and histology biomarker analysis in the support of Clinical Trials.

The network provides you with access to scientists of all laboratory specializations within our organization and allows us to provide highly consultative services. Eurofins is unparalleled in its portfolio of testing, its innovative technology and its history of having a global presence.

## PROTEIN BIOMARKER ANALYSIS

| CAPABILITY | TECHNICAL PRINCIPLE | INSTRUMENT PLATFORM |
|---|---|---|
| High Throughput Modular Analysis | Colorimetry, Enzymology, Turbidimetry, ISE, Electro Chemiluminescence Immunoassay | Cobas 6000, Cobas 8000 |
| Nephelometry | Immunonephelometry | BN ProSpec |
| Spectrophotometric | UV, visible light, IR Plate Readers | Spectramax, Specord PC210, Infinite M200 |
| Binding Assays | EIA, ELISA | DSX Best2000, Behring ELISA processor, Evolis, Freedom Evolyzer, Biotek Epoch Universal Plate Reader, Biotek Synergy 2, Perkin Elmer 2104 Envision Reader, Hamilton Microlabstar, MolDev Versamax, MolDev Spectramax M5, Fluostar Omega |
| Binding Assays | ImmunoCAP, EliA, Fluoroenzymeimmunoassay | Phadia 100, Phadia 250 |
| Binding Assays | RIA | Perkin Elmer Gamma Counter, Perkin Elmer Wizard 1470-020 |
| Immunoassays | MSD | MSD 600, MSD 2400, MSD SQ120 |
| Immunoassays | Singulex Digital ELISA | Erenna Ultrasensitive Immunoassay Platform |
| Immunoassays | Luminometry, Bead-based multiplexing | Luminex 100, Luminex 200, Luminex MAGPIX |
| Immunoassays | Gyros Microfluidics | Gyrolab xP |
| Coagulation | | BCS XP, CS5100, BSC, CA 560 |
| Immunochemistry | | Advia Centaur XP, Liaison, Kryptor |
| Flow Cytometry | Cell Based Assays | FACS Canto II, Beckman Coulter FC500 |

## GENOMIC BIOMARKER ANALYSIS

| CAPABILITY | TECHNICAL PRINCIPLE | INSTRUMENT PLATFORM |
|---|---|---|
| Genotyping | qPCR, Sanger Sequencing based genotyping, PCR SSO, Multiplex PCR, RFLP PCR, Bisulfite methyl PCR | Thermofisher 3130 XL DNA Analyzer, ThermoFisher 3730XL DNA Analyzer, Roche Lightcycler LC 480 and 480 II, ThermoFisher ABI7500, MR.SPOT (Bag Health Care), Biocartis Idylla, PCR analyzers |
| HT Genotyping | Microfluidics | Fluidigm Biomark |
| HT Genotyping | SNP Array Technology | Affymetrix 3000 G7, GeneTitan, Illumina iScan |
| Gene Expression | qRT-PCR, Nanostring | Roche Lightcycler LC 480 II, Nanostring nCounter |
| HT Gene Expression | Microfluidics | Fluidigm Biomark |
| HT Gene Expression | Micro Array Technology | Affymetrix 3000 G7, GeneTitan, Illumina iScan |
| Sequencing Analysis | Pyrosequencing | Qiagen Pyromark Q24 |
| Next Generation Sequencing [NGS] | Exome Sequencing including FFPE and deep sequencing, Methylation Sequencing, Targeted panels - Cancer MiSeq, RNA Sequencing, Single Cell Sequencing | Illumina MiSeq, Illumina HiSeq 2500, Illumina HiSeq 4000, Illumina NextSeq 500, ABI 3730 XL96/ABI3100/ABI3130 |

## HISTOLOGY BIOMARKER ANALYSIS

| CAPABILITY | TECHNICAL PRINCIPLE | INSTRUMENT PLATFORM |
|---|---|---|
| Cytology | Automated slide preparation system | CYTYC THIN PREP 2000, Hologic TP 2000, Hologic TP 5000 |
| Histology | Tissue processors, Multiple Slide Stainer | Sakura VIP 200, Sakura VIP E300V, Sakura DRS 2000 |
| IHC | Automated horizontal slide-processing system for immunostaining, Automated IHC/ISH slide staining system | Dako Autostainer Plus S3800-7635, Ventana BenchMark ULTRA |
| Imaging | Imaging sytem | Hologic IMAGING STATION |


SCIENTIFIC CONSULTING
• Assay Feasibility
• Assay Suitability
• Validation Requirements
• Regulatory Compliance
• Multiplexing
ASSAY DEVELOPMENT AND VALIDATION
• GLP and GLP-like Method Development & Validation
• Commercial Kits
• Fit for Purpose Validation from CLIA to Advanced Validation
HIGH THROUGHPUT BIOMARKER TESTING
• Global Kit Production
• Global Sample Management
• Central Laboratory Analysis
• Central Laboratory Reporting

# Validate versus Verify

The Eurofins Central Laboratory biomarker validation procedures are fit-for-purpose and may range from CLIA verification to advanced validation of biomarker assays. For method validation of biomarker assays, a distinction will be made between [1] biomarker data for exploratory purposes and [2] biomarker data in support of efficacy/safety decisions for regulatory purposes.

## Category 1

Purpose: exploratory assessments of biomarker data (e.g. internal decision-making, understanding of pharmacodynamics [PD] or Mechanism of Action) and not drive label claims. This method validation exercise can be extended as deemed necessary, depending on the intended purpose of the data.

- **Category 1A:** in vitro diagnostics (IVD); CE marked or FDA cleared assays; verification of manufacturer's claim according to the CLSI/CLIA guidelines.
- **Category 1B:** Research Use Only (RUO) assays, fit-for-purpose approach by validating at the evel of sensitivity, precision and accuracy on kit controls and precision on matrix samples of the disease state. Stability assessment can be considered on a case-by-case basis.

## Category 2

Purpose: biomarker data used for pivotal safety and efficacy decisions in clinical development (intended for dosing/drug approval or labelling; data will be submitted to a regulatory agency).

For biomarkers assays intended for drug approval, the same questions need to be addressed as for an assay intended to measure drug concentration and therefore a similar validation approach as for pharmacokinetic (PK) assays should be performed.

As such, the acceptance criteria as described in current FDA/EMA guidelines for bioanalytical method validation should be applied, where and when possible. Clinical biomarkers are not subject to GLP standards, but they should be considered and validated therefore as as "fit-for-purpose" assays, meaning that the standard process for GLP validation should serve as the framework for the validation of biomarker assays as well.

At Eurofins Central Laboratory, our biomarker method development and method validation processes are in compliance with CLIA, FDA and EMA guidelines and published recommendations on biomarker assay validation.

Mark E. Arnold, Brian Booth, Lindsay King, Chad Ray.
Workshop report: Crystal City VI-Bioanalytical Method Validation for Biomarkers.
Published Online 11 august 2016. The AAPS Journal. DOI: 10.1208/s12248-016-9946-6.

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# RESULTS THAT MATTER

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