MEDPACE

UNDERSTANDING REGULATION AND VALIDATION PROCESSES FOR BIOMARKERS

and the Benefit of an Experienced Partner for Biomarker Strategy

In today's evolving clinical landscape, navigating the complex regulations, standards, and validation processes for biomarkers requires not only scientific precision but also strategic insight. In this Q&A, Medpace regulatory and scientific experts share critical considerations to ensure biomarker success.

REGULATIONS AND STANDARDS

What regulations and guidelines do Medpace's central laboratories follow?

Medpace follows Good Clinical Practice (GCP) and Clinical Laboratory Improvement Amendments (CLIA) regulations. For standards, we follow Good Clinical Laboratory Practice (GCLP) and College of American Pathologists (CAP).

What are the GCLP guidelines?

GCLP is a combination of GCP and Good Laboratory Practice (GLP) regulations from the generic best practice (GxP) guidelines created by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). In 2003, the Research Quality Association (RQA) suggested a new guideline. Later the World Health Organization (WHO) and the British Medicines and Healthcare Products Regulatory Agency issued their versions of a GCLP guideline. For central labs, we use the WHO guidance.

Why were the GCLP guidelines created?

Labs working in clinical trials needed a unique set of standards. The GLP regulations did not include unique guidelines for laboratory samples from clinical studies. Therefore, a hybrid standard, or the GCLP standards, was created to fill in the gap between pre-clinical and clinical research trials.

Is GCLP a regulation?

It's important to note that GCLP is not a regulation. A regulation is a government law that states what we must follow. GCLP is a set of standards recognized globally. Medpace references these GCLP guidelines for clinical trial activities associated with laboratory work.

What are the CLSI and BMV guidelines?

CLSI documents are standards from the Clinical & Laboratory Standards Institute (CLSI) used for testing the quality, safety, and efficiency of biomarker assays. The FDA Bioanalytical Method Validation (BMV) guidance document helps Sponsors with investigational new drug applications and are used to validate bioanalytical methods used in pre-clinical and clinical research.

Depending on whether a biomarker is a primary, secondary, or exploratory endpoint, helps determine which analytical method process is chosen and how it is validated. A primary or secondary endpoint may require full method validation following CLIA and FDA regulations. An exploratory endpoint may only require a fit for purpose validation, which can be as simple as doing analytical measurement range (AMR), precision, accuracy, and stability according to CLSI, CAP, or BMV guidelines. Medpace will consult with the study Sponsor on the most appropriate approach for a given study and biomarker based on the intended purpose of the resulting data.

What guidelines do we follow for validations?

For validations, Medpace central laboratories follow CAP, GCLP, and CLSI guidelines, which incorporate much of the 2025 BMV guidelines.

Does the FDA require that biomarkers follow the BMV guidance?

Yes, the FDA requires that the biomarker development needs to follow the BMV guidance, which Medpace incorporates in both our central and bioanalytical laboratory validations.

Is there an overlap between the guidelines and regulations?

Yes, most guidelines are based on regulations with additional detail or to fill in potential gaps to ensure a more globally standard approach to whoever is doing the associated process or work.

What is a CAP laboratory?

A CAP laboratory is a medical laboratory that is accredited by the College of American Pathologists (CAP), a leading accreditation body in the US for laboratory quality assurance and improvement. Both US and international laboratories can have CAP accreditation.

What is a CLIA laboratory?

The Clinical Laboratory Improvement Amendments (CLIA) regulations are used for any US laboratory which tests patient samples and provide individual results to a physician for the treatment, diagnosis, or assessment of that patient. These regulations require an external verification, like The College of American Pathologists (CAP), to ensure consistency in testing and processes. The regulations directly reference CAP, although there are other agencies / companies which can be used to provide proficiency testing results.

Is CLIA a requirement for all lab work?

In the United States, a CLIA accredited laboratory is required to be used if the results are going back to a clinician who may treat, diagnosis, or assess the patient based on the laboratory results. Testing can be performed at a non-CLIA laboratory if the results are going back to the Sponsor as study data but not to the clinician at the site.

Are there exceptions to this rule?

Yes, there are exceptions. Academic laboratories may be used in early phase studies where data goes back to the clinician. Congress passed the CLIA '88 law for clinical, diagnostic, and medical labs. But the FDA oversees everything else, such as drug manufacturing, manufacturing of medical devices, clinical trials pertaining to pre-marketing analysis.

Given that Medpace is global, do all our labs follow all the same regulations?

Yes, all Medpace's global central lab locations follow GCP. Labs outside the US are not required to have CLIA accreditation, although all Medpace central lab locations follow CAP standards and are CAP accredited. The Medpace US and Belgium laboratories are also ISO15189 certified.

What is ISO15189 certification?

Labs pursue ISO15189 certification to demonstrate that they meet internationally recognized standards for quality. ISO15189 requires the laboratory has a quality management system and technical requirements necessary to ensure accurate and reliable test results, consistent laboratory operations, and proper handling of patient samples and data.

Are there additional regulations in other countries that we must follow?

Yes, there may be additional country-specific regulations that are required, and Medpace follows those requirements. For example, some countries require that certain testing (e.g. TB, drugs of abuse, HIV testing) be performed only at government affiliated laboratories.

Are there other agencies like the FDA that Medpace must follow regulations?

Yes. Examples include the EMA, NMPA, PMA, and ANVISA. These agencies require the same basic principles of GCP.

Is GLP for non-human trials?

Yes, GLP regulations are specifically for non-clinical trial submissions to the FDA and Environmental Protection Agency (EPA).

When should a bioanalytical laboratory vs. a central laboratory be used?

It is a case-by-case basis that depends on the Sponsor's goals and feedback from the FDA or other regulatory agencies. A primary or secondary endpoint could be performed by either the central or bioanalytical lab. If the analyte being tested is required on a laboratory report going to sites in the US, then a CLIA accredited lab should be used (normally a central laboratory). If the analyte requires testing under the GLP, then the testing should be completed in a lab that follows GLP regulations (normally a bioanalytical lab).

Why is it essential to have an experienced lab team?

An experienced team will know the regulations and guidelines. A good lab team will guide their Sponsors and ensure they are following the right laws without adding unnecessary processes.

How do we help Sponsors understand the different guidelines, regulations, and accreditations?

Medpace has many biotech Sponsors who may have only worked in research on discovery, or pre-clinical trials. For them, it may be the first time they have designed a clinical development program. Since many are aware of GLP regulations from their pre-clinical research, they can be concerned about fulfilling regulations and following the right guidelines when they advance their program into clinical trials.

Medpace can help our Sponsors understand the different regulations and guidelines. Depending on the Sponsor's needs, and the biomarkers they're working with, which determines the type of regulations and guidelines need to be followed. Medpace Regulatory Affairs team provides comprehensive international regulatory support at all stages of the drug development process.

IVDR IN EUROPE

What is IVDR?

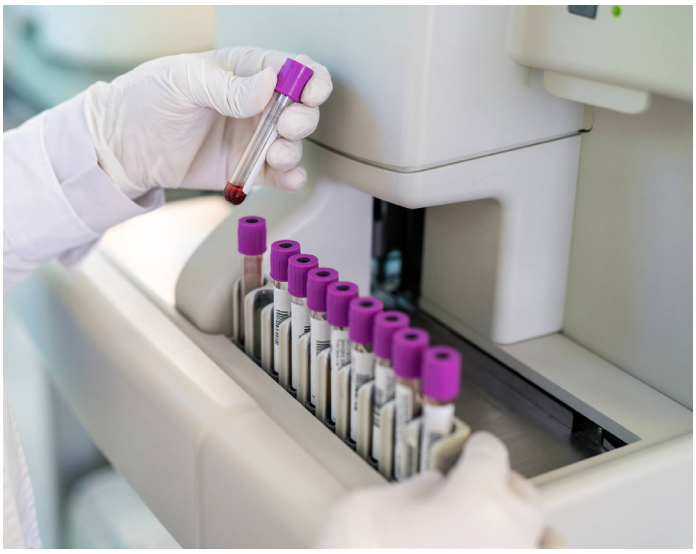
The European Union implemented Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) to improve clinical safety for patients. The IVDR replaced the existing Directive 98/79/EC on in vitro diagnostic medical devices (IVDD) and became effective on 26 May 2022. It is a regulatory framework that introduced new requirements for marketing, certification, and performance studies of in vitro diagnostic (IVD) medical devices for human use.

Does IVDR impact clinical trials?

The IVDR applies to all testing that will be used for medical management of individuals residing in the European Economic Area (EEA) regardless of where the laboratory is located. Turkish medical device legislation is similarly aligned. This includes assays used for inclusion and exclusion of subjects, treatment allocation as well as monitoring the safety and efficacy of the treatment during the trial.

What is an IVD?

Briefly, it covers all assays performed on human samples, sample collection devices, companion diagnostics, and software intended to detect disease or to provide information about the medical condition of an individual. Typically, IVDs have a medical application or a medical purpose.



Can existing IVDs still be used under IVDR?

IVDR provides a transition period where products approved under the previous Directive and the new Regulation are simultaneously allowed on the market. The majority of devices that were previously approved under IVDD cannot be grandfathered into IVDR and will require a formal Conformity Assessment by a Notified Body to comply with IVDR beyond the transition period.

What are the timelines for IVDR compliance?

Due to the large number of new Conformity Assessments and the limited capacity of Notified Bodies within the Union, a gradual roll-out of the Regulation was needed to avoid shortages of essential IVDs and to protect public health. Devices that already received a Certificate of Conformity or Declaration of Conformity in accordance with the previous IVDD Directive can remain on the market under certain conditions. Highest-risk devices (class D) must be approved under IVDR by 31 Dec 2027, while devices in the lowest risk class can be placed on the market until 31 Dec 2029 if the manufacturer complies with the requirements for transition to IVDR. Most biomarker assays used at Medpace central laboratories are class C or lower risk devices (class B) and the majority of manufacturers are committed to transitioning their biomarker portfolio.

Are all CE-IVD assays compliant with IVDR?

CE-marked IVDs must be used according to their approved intended use to comply with the Regulation. In addition, if a manufacturer has not started the transition process for IVDR by the applicable deadlines, IVDs that received a CE-label under the previous IVDD Directive can no longer be placed on the market with a CE-label after the end of their transition period. They may still be marketed for Research Use Only (RUO) past this point.

Can I use devices without a CE mark for biomarker testing of EU patients?

Products for general laboratory use and RUO products are exempt from IVDR if their use in the trial does not meet the definition of an IVD. Results from such products must be used exclusively for exploratory endpoints or other non-medical purposes such as retrospective analysis without impact on patient treatment.

For non-CE marked IVDs (or when CE-marked IVDs are used for a medical purpose outside their intended use) the Sponsor must either conduct a performance study or testing must be performed at a Health Institution within the EU as an 'In-House IVD', provided that the requirements in IVDR Article 5 (5) are met.

VALIDATION PROCESS FOR CENTRAL LABS

What is a validation plan, and why is it important?

The validation plan defines the experiments that we're going to complete for the analytical method and states the expected acceptance criteria, which will tell us if the validation was successful.

Do you have some idea of what you need to see to consider it a successful experiment?

Yes, each experiment will have criteria set that it must pass, or the bare minimum for it to be acceptable. Those criteria may include: precision, accuracy, analytical measuring range, sensitivity, reference range, interfering substances, and stability.

Who writes up the validation plan?

The Medical Technologist that will be performing the validation will write the validation plan. It is reviewed by the PhD Scientist (or Analytical Project Manager) that is overseeing the validation. The PhD Scientist is assigned based on their area of specialty (e.g. molecular, flow cytometry, immunoassay, coagulation, chemistry).

After the validation plan is written and reviewed, where does it go?

After the laboratory finishes its review, the plan goes to QA for review and auditing. After QA review, it goes to the laboratory director for signature. Once it is returned to the laboratory, the Scientist or Analytical Project Manager does a final sign-off. Once the plan is approved, the validation experiments can begin.

How long is our turnaround timeline?

Turnaround time is variable depending on the complexity of the validation. On average, it's 10 to 12 weeks from the beginning of the validation plan until the end when the validation report is complete, the SOP written, and the lab staff trained.

What are the types of validations Medpace can do?

Medpace has two main categories for validations. The first is a limited validation, that is used with an established assay that's already been approved by the European Medicines Association (EMA), or the FDA, and has 510(K) clearance.

The second category is used for assay developed de novo, and it has more stringent requirements, including additional testing for robustness of the experiment. For example, longer term stability, freeze thaw stability, interference testing.

What's involved with feasibility?

Feasibility testing takes place before a validation starts and is required only if we're developing an assay from scratch, or de novo.

When is the validation report written?

After the validation experiments are complete, a validation report is written. The validation report describes the validation procedures, data obtained, evaluations, and comments observed during the validation. The report compares the result metrics to what the validation plan defined as a successful outcome and states if each experiment was successful.

Who writes the validation report?

The Medical Technologist that performed the validation experiments writes the validation report. The Scientist that oversaw the validation reviews, edits, and comments on the report. The Scientist may provide feedback to the Medical Technologist to perform additional validation experiments, repeat testing, or add more information to the report.

After the validation report is reviewed by the lab personnel, where does it go?

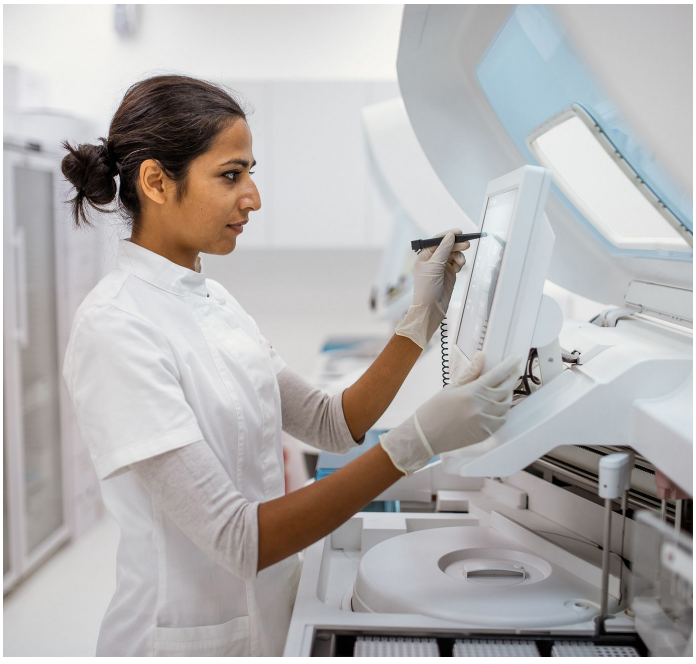
A printout or electronic copy of the completed Validation Report is submitted to the Laboratory Director for approval. Raw data of all experiments are attached to the validation file for future reference. The Laboratory Director may request that a part of the validation be repeated, or that additional validation testing be performed. In such cases, the Validation Plan is updated, the requested validation testing is carried out, and the Validation Report is completed and resubmitted for approval. After the Validation Report is approved by the Laboratory Director, the report is submitted to Quality Assurance for independent review.

THE BENEFIT OF AN EXPERIENCED PARTNER

What's the importance of having a team of PhD scientists?

The PhD scientists are integral to Medpace's scientific consulting service. Early engagement with the Sponsor and their scientists goes a long way if we're involved early on because Medpace knows how to manage biomarkers within clinical trials. Our PhDs are experts at testing biomarkers for clinical studies. Our scientists will guide Sponsors who may only have a GLP (pre-clinical) background to understand the requirements for clinical work.

In the exploratory phase of the program, Sponsors may have been using an academic research center that's developed an assay or come up with a method to measure a biomarker. But then as they move along in the clinical development program, that assay needs to become more robust. For example, a Sponsor was doing some exploratory flow cytometry work in research before they came to Medpace. They then asked to transfer the method to Medpace. Our scientists were able to make sure that the analytical method was robust, and that the lab was measuring the biomarkers to meet regulatory requirements and industry expectations.



In addition to having experienced Medical Technologists, how do PhD scientists ensure quality?

Having experienced Medical Technologists is very important. They are the key personnel that are doing the actual testing and reviewing results. The PhDs provide additional oversight of the testing process by providing regulatory guidance and leading the team on problem-solving. The scientists have an in-depth understanding of the actual molecule being measured and how it applies in physiology. For example, our flow cytometry scientists are PhDs in immunology or immunobiology, and they understand the immune system and how it works along with having an in-depth understanding of the method.

How important is it for central labs to be integrated with Medpace CRO?

Medpace's central laboratories, along with our CRO, are a key part of Medpace's management of clinical trials. Sponsors that work with Medpace clearly see how the lab and CRO work seamlessly together. The clinical operations, regulatory affairs, and central labs all use the same or integrated IT systems, have operational efficiencies between the teams, and have access to the best medical and scientific experts in the industry.

A key advantage for Sponsors, is having access to Medpace's medical experts that work closely with central labs and our PhD team. The medical team can provide invaluable information from the clinical side. They have experience seeing and treating patients and are experts in their medical therapeutic areas. These medical doctors provide our Sponsors recommendations on what biomarkers should be selected for each disease indication. The medical team collaborates closely with the laboratory PhDs, discussing proper methodology to use for measuring the biomarkers.

Why is it essential for Sponsors to get a lab partner involved early on?

Engagement between the laboratory scientists and the Sponsor early is very important. Early dialogue can lead to good biomarker and methodology decisions that, in the end, save money, reduce study timelines, and ensure robust study data for FDA submission. Medpace has performed over a thousand clinical trials, so the team sees a lot of clinical protocols for the same indications, and our scientists can guide Sponsors.

Medpace regularly works with the FDA and helps our Sponsors to prepare for pre-IND meetings. Pre-IND meetings are usually critical, and that's where the Sponsor gets a lot of feedback on their project. Working with a partner early on can be invaluable for Sponsors because they can get the right guidance they need early on.

Is Medpace the right partner for biomarkers?

Yes. Medpace has the capabilities and scientific expertise to provide biomarker solutions for our Sponsors. From exploratory biomarkers to primary biomarkers, from established methods and kits to those that need to be developed de novo Medpace has the team with the scientific expertise to do it. Medpace's mission is to accelerate the global development of safe and effective medical therapies. Medpace's dedicated teams in both in our laboratories and in our CRO serve as an extension of your team. We engage quickly and provide strategic thinking, ensure quicker start-up times, provide superior quality, and the most efficient delivery of every phase of your clinical trial. Our laboratory, therapeutic and regulatory experts are committed to streamlining your path to approval, so every partnership is designed to create research solutions focused on your critical needs.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.