MakroCare
New Possibilities, Everyday

WHITEPAPER

# Scientific Analysis and Validation for IVDs: An Overview and Guide

www.makrocare.com

medtech@makrocare.com

IVD typically stands for "In Vitro Diagnostics". These are medical devices and diagnostic tools used to perform tests on bodily samples such as blood, urine, or tissue collected from the human body. These tests are conducted outside of the body in a controlled laboratory environment. In vitro diagnostics play a crucial role in disease detection, monitoring, and management. They encompass a wide range of tests including infectious diseases, cancer markers, genetic testing, and various other conditions.

Under the IVDR, biomarkers and analytes are subject to classification based on their intended purpose, risk level, and impact on patient management. Manufacturers must classify biomarkers and analytes in accordance with the IVDR classification rules to determine the applicable conformity assessment procedures.

This classification is intended to define the assessment process and the conformity procedure to be followed for each IVD. A highest-risk IVD is defined as having the greatest potential of impacting patient safety compared to high, moderate and low risk devices. Hence, the submission for the highest-risk IVD will be assessed more critically before it is approved to be placed in the market.

## Classification of the IVDs into Class A, B, C or D:

Class A (Low risk): Products for general laboratory use such as instruments, buffer solutions, washing solutions, and general culture media and histological stains.

Class B (Moderate risk): Self-testing devices for detection of pregnancy, fertility testing, level of cholesterol, glucose, erythrocytes, leucocytes, and bacteria in urine.

Class C (High risk): Analytes for other blood grouping (not covered by Class D) such as for foetomaternal blood group meant for transfusion, transplantation, or cell administration. Analytes for sexual transmitted disease, infectious disease, congenital disorders companion diagnostics analytes for disease staging including cancer diagnosis and staging human genetic testing patient management by monitoring level of medicinal products self-testing devices.

Class D (Highest risk): Analytes for life-threatening conditions those transmissible in blood and biological matter meant for transfusion, transplantation, or cell administration blood grouping markers of ABO, Rhesus, Kell, Kidd, and Duffy system.

## Regulatory:

IVDs are subjected to regulatory oversight by agencies such as the FDA in the United States or the European Medicines Agency (EMA) in Europe. These agencies require manufacturers to provide evidence of analytical and clinical performance through rigorous scientific analysis and validation studies before a test can be approved for clinical use.

## European Regulation IVDR 2017/746:

The new European Regulation IVDR 2017/746 is far stricter. While strengthening the requirements of the IVDD, it provides greater detail and clear guidelines for conducting performance evaluations of IVD products. The intention for these changes is to bring in better regulatory control to enhance and safeguard patient safety. Thus, compliance to the EU IVDR and the CE marking regulation involves proving compliance not only to the GSPRs (General Safety and Performance Requirements), but it also mandates conducting a premarket performance evaluation.

## USFDA Regulation:

IVDs are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to section 351 of the Public Health Service Act. Like other medical devices,

IVDs are subject to pre-market and post-market controls. IVDs are generally also subject to categorization under the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.

FDA classifies IVD products, into class I, II, III according to the level of regulatory control that is necessary to reasonably assure safety and effectiveness.

General Controls are the basic provisions (authorities) of the May 28, 1976 Medical Device Amendments to the FD&C Act, that provide the FDA with the means of regulating devices to reasonably assure their safety and effectiveness.

A 510(k) is a premarket submission made to the FDA to demonstrate that the device to be marketed at least as safe and effective, that is, substantially equivalent (SE), to a legally marketed device.

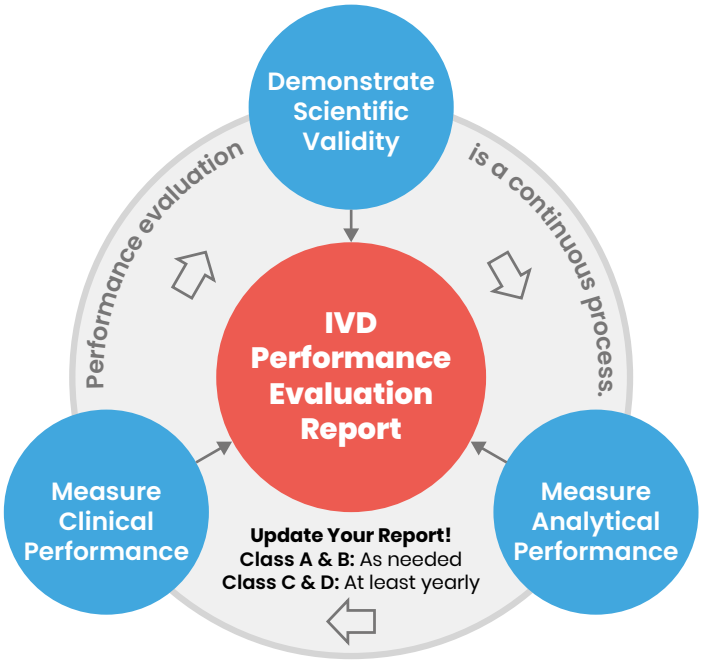
De Novo classification is a risk-based classification process. Devices that are classified into class I or class II through a De Novo Classification Request (De Novo request) may be marketed and used as predicates for future premarket notification [510(k)] submissions, if necessary.

## Performance Evaluation of IVDs:

The IVDR defines Performance Evaluation in article 2 as:

Performance Evaluation must demonstrate the following three aspects newly introduced by the IVDR (Article 56 and Annex XIII):

1. Scientific Validity of an analyte means the association of the analyte with a clinical condition or physiological state. For example, the spike protein of Corona virus is an analyte linked to a detection of infection that causes COVID-19. For established analytes like hemoglobin, enough data exists to correlate it to anemia. But for new biomarkers, the scientific validity needs to be established.




2. Analytical Performance means the ability of a device to correctly detect or measure a particular analyte. This is done by the manufacturer during the design and development phase.

3. Clinical Performance means the ability of a device to yield results that are correlated with a particular clinical condition, a physiological or pathological process, or in accordance with the target population and intended user.

The approach taken by the IVDR is a logical one. It requires manufacturers to establish the scientific correlation of the analyte, determine its analytical performance, and then validate it clinically in relation to the current state of the art. Sufficient and quality data has to be collected for demonstrating safety, performance, and notably the acceptability of the benefit-risk ratio. The data should be thorough and objective, and it should take into account any favourable and unfavourable situations which we could see in real life. The results are analyzed, interpreted, and concluded in the Performance Evaluation Report to make a decision on the benefit-risk ratio. This constitutes the Clinical Evidence for a device, supports the use of the device, and takes into consideration the current state of the art.

## IVD CE Marking:

For all IVD devices except Class A (non-sterile), your QMS and Technical Documentation must undergo an audit with a Notified Body, an independent third-party conformity assessment body designated by European national authorities to carry out audits on medical device companies and products within the meaning of applicable EU legislation.

For Class A (non-sterile) IVD devices, there is no Notified Body intervention.

## Validation of IVDs:

1. **Analytical Sensitivity:** This refers to the ability of the test to detect low concentrations of the analyte in a sample. Analytical sensitivity is typically determined by measuring the lowest concentration of the analyte that can be reliably detected by the test.
2. **Analytical Specificity:** Analytical specificity assesses the ability of the test to accurately identify the target analyte without interference from other substances present in the sample. Specificity studies may involve testing the IVD with samples containing potential interfering substances to evaluate its selectivity.
3. **Accuracy:** Accuracy measures how closely the test results reflect the true value of the analyte concentration. It encompasses both analytical sensitivity and specificity and is typically assessed by comparing the test results to a reference method or known standard.
4. **Precision:** Precision evaluates the consistency and reproducibility of the test results when the same sample is tested multiple times. Precision studies assess both within-run (repeatability) and between-run (reproducibility) variation to ensure consistent performance of the IVD.
5. **Linearity:** Linearity assesses the ability of the test to produce results that are directly proportional to the concentration of the analyte in the sample. Linearity studies involve testing samples with varying concentrations of the analyte to determine the linear range of the assay.
6. **Limit of Detection (LOD) and Limit of Quantification (LOQ):** LOD and LOQ represent the lowest concentration of the analyte that can be reliably detected and quantified by the test, respectively. Determining these limits is essential for establishing the sensitivity and utility of the assay.
7. **Stability:** Stability studies assess the robustness of the IVD under various storage and environmental conditions. This includes evaluating the stability of reagents, calibrators, and controls, as well as the test platform itself, to ensure consistent performance over time.
8. **Cross-reactivity and Interference:** Cross-reactivity studies evaluate the potential for the test to produce false-positive results due to the presence of similar analytes or substances in the sample. Interference studies assess the impact of interfering substances on the accuracy and specificity of the test results.
9. **Matrix Effects:** Matrix effects refer to variations in test performance caused by differences in sample matrices (e.g., blood, serum, plasma). Evaluating matrix effects is important for ensuring the reliability and applicability of the test across different sample types.
10. **Statistical Analysis:** Statistical methods are employed to analyze the data generated from scientific analysis studies, including determination of sensitivity, specificity, accuracy, precision, and other performance parameters. Common statistical techniques include regression analysis, receiver operating characteristic (ROC) curve analysis, and calculation of confidence intervals.

By conducting rigorous scientific analysis studies, manufacturers can thoroughly evaluate the performance characteristics of IVDs and ensure their reliability and accuracy for clinical use. These studies provide essential data for regulatory submissions and help to establish the validity and utility of the diagnostic test in medical practice.

*******