



How to demonstrate clinical performance

WHITE PAPER



Introduction to IVDR

The introduction of the European Union In Vitro Diagnostic Medical Devices Regulation (IVDR) 2017/746 brings new and increased safety and performance requirements for devices which In Vitro Diagnostic (IVD) manufacturers must comply with to continue marketing within the European Union (EU) market.

A device can be placed on the market or put into service only if it complies with the regulation when used in accordance with its intended purpose. A device must comply with the General Safety and Performance Requirements (GSPRs) outlined in the IVDR. To demonstrate conformity with these GSPRs, a performance evaluation must be conducted.

Many manufacturers have placed devices on the market under the EU In Vitro Diagnostic Medical Devices Directive (IVDD) before the IVDR came into force. A legacy device is an IVD device that was placed on the market under the previous IVDD prior to the IVDR date of application (May 26, 2022) and continues to be available during this transitional period. To be compliant with IVDR requirements, manufacturers must submit their own evaluation of their device's performance as part of the conformity assessment process carried out by a Notified Body.

Clinical evidence and State of The Art (SoTA)

The IVDR requires that performance evaluation demonstrates:

- Scientific validity: the association of an analyte with a clinical condition or a physiological state
- Analytical performance: the ability of a device to correctly detect or measure a particular analyte
- Clinical performance: the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in line with the target population and intended user

Confirmation of conformity with relevant GSPRs must be supported by scientific validity, as well as data on analytical and clinical performance, providing sufficient clinical evidence. This includes, where applicable, relevant data to demonstrate compliance with the necessary safety and performance standards. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant GSPRs. That level of clinical evidence must be appropriate considering the characteristics of the device and its intended purpose.

Scientific validity and analytical performance may have similar levels of detail across different device types, as they do not directly depend on the risk class. Clinical performance, on the other hand, is directly linked to the risks associated with the use of the device for individuals or public health. For this reason, the level of detail required for clinical performance varies across device classes. Devices with a higher risk class require greater evidence of clinical performance:

Class D > Class C > Class B.

Common Specifications (CS) are provided for certain devices, as outlined in Commission Implementing Regulation (EU) 2022/1107, which lays down common specifications for certain Class D in vitro diagnostic medical devices. Clinical evidence must be demonstrated while considering these as minimum requirements.

The data and conclusions drawn from the assessment of these elements constitute the clinical evidence for the device. It must scientifically demonstrate—by reference to the state of the art in medicine — that the intended clinical benefit(s) will be achieved and that the device is safe and meets performance requirements.





Clinical evidence is a continuous process that must be updated throughout a device's lifecycle. Device performance evaluation should be periodically reassessed to verify that it still satisfies GSPRs, its intended purpose, and the state of the art.

State of the Art is not defined in the IVDR; however, in MDCG 2022-2, it is described as: *"Developed stage of current technical capability and/or accepted clinical practice in regard to products, processes, and patient management, based on the relevant consolidated findings of science, technology, and experience."*

It is crucial to note that SoTA is a time-sensitive concept. This is especially important for legacy devices, as manufacturers must maintain up-to-date clinical evidence based on the current state of the art. What was valid during the development or validation of a legacy device may no longer be valid today.

Clinical evidence documentation

Specific documentation, as stated in *Annex XIII, Part A*, must be prepared to demonstrate compliance with the regulation, including:

- Performance Evaluation Plan (PEP, *Annex XIII 1.1*): Specifies the characteristics and performance of the device, as well as the process and criteria applied to generate the necessary clinical evidence
- Scientific Validity Report (SVR, *Annex XIII 1.2.1*): Demonstrates and documents the relationship between an analyte and a specific physiological or pathological state
- Analytical Performance Report (APR, *Annex XIII 1.2.2*): Demonstrates and documents the analytical performance of the device

- Clinical Performance Report (CPR, *Annex XIII 1.2.3*): Demonstrates and documents the clinical performance of the device
- Performance Evaluation Report (PER, *Annex XIII 1.3*): Includes the scientific validity report (SVR), the analytical performance report (APR), the clinical performance report (CPR), and an assessment of these reports, allowing for the demonstration of clinical evidence

This documentation is always required during device conformity assessments by the Notified Body. A manufacturer should perform a gap analysis of any evidence collected for their legacy device to determine which information supports GSPRs and which data or studies must be completed to achieve IVDR compliance through new studies.

Benefit-risk analysis

For each device, a benefit-risk analysis should be conducted based on GSPRs 1–8 in *Annex I, Chapter 1*, which apply to all IVD devices.

To be considered acceptable, the analysis must demonstrate that the benefits of using the device for its intended purpose outweigh the risks. The analysis may be both qualitative and quantitative, considering relevant guidelines and standards.

Evidence of the benefit-risk analysis and proof that a risk management system has been implemented must be traceable throughout the technical documentation.



Clinical performance

The clinical performance aims to prove that the IVD can deliver clinically relevant results through consistent, predictable and reliable use by the intended users within its use environment. The manufacturer must provide evidence that the IVD has been tested for the intended uses, target populations, usage conditions, with all the intended user groups and within the operating and use environments.

Indicators of clinical performance vary and depend strongly on the intended purpose and performance claims. The IVDR identifies key clinical parameters as follows:

- Diagnostic sensitivity: ability of a device to identify the presence of a target marker associated with a particular disease or condition
- Diagnostic specificity: ability of a device to recognize the absence of a target marker associated with a particular disease or condition

- Positive predictive value: ability of a device to separate true positive results from false positive results for a given attribute in a given population
- Negative predictive value: ability of a device to separate true negative results from false negative results for a given attribute in a given population
- Likelihood ratio: likelihood of a given result arising in an individual with the target clinical condition or physiological state compared to the likelihood of the same result arising in an individual without that clinical condition or physiological state
- Expected values in normal and affected populations

All of these parameters should be demonstrated unless justification is provided explaining why they are not applicable.

Based on the type of device, if other parameters may be more appropriate, then the performance of which should be demonstrated within the clinical evidence.

Clinical performance: sources

The IVDR identifies three main sources to demonstrate the clinical performance of a device:

- Clinical performance studies
- Scientific peer-reviewed literature
- Published experience gained through routine diagnostic testing

It is important to note that, as stated in *Annex XIII 1.2.3* of the IVDR:

"Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data."

For new devices and novel analytes, clinical performance studies are almost always conducted to demonstrate clinical performance. Conversely, for legacy devices, clinical performance data is often already available. Studies conducted before the IVDR came into force that do not meet the regulation's requirements for clinical performance studies are considered other sources of clinical evidence.



Clinical performance studies

The purpose of Clinical Performance Studies (CPS) is to establish or confirm the ability of the device to diagnose, monitor, or predict a clinical condition, including aspects of device performance that cannot be determined by analytical performance studies, literature, or previous experience gained through routine diagnostic testing.

A clinical performance study under the IVDR requires a Clinical Performance Study Protocol (CPSP) and a Clinical Performance Study Report (CPSR).

A CPSP should consider all the following, if relevant:

- Study rationale and objectives, considering standards and common specifications
- IVD under evaluation and comparator device (if applicable)
- State of the Art (SoTA)
- Target population, sample size, specimen type and collection, inclusion and exclusion criteria
- Study method, ethics considerations and approval, equipment, personnel training
- Usability, especially for self-test or near-patient testing devices

- Data analysis, statistical methods, outlier handling, and acceptance criteria
- Study sites, monitoring and deviations tracking
- Benefit-risk analysis

A CPSR should address all the considerations above, including a critical analysis of the results, taking into account both positive and negative aspects. It should also state the clinical performance achieved, with justification if any required elements are not present. Comparative studies, using a comparator device already on the market, are common and serve as an excellent way to demonstrate the clinical performance of the device under study in a real-world environment and by the intended user.

The harmonized standards to consider when designing and executing a CPS include:

- EN ISO 14155:2020 – Clinical investigation of medical devices for human subjects
- EN ISO 20916:2024 – In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects, good study practice



Scientific peer-reviewed literature

An objective, non-biased, systematic search and review method should be used to identify both favorable and unfavorable data for the device under evaluation.

Scientific peer-reviewed literature can be used as the main source of clinical performance evidence for legacy devices, often in conjunction with other methods.

To provide ideal evidence, publications should involve the device under evaluation. Publications can be used to support the device's:

- Clinical performance claims
- State of the Art (SoTA)
- Intended user and/or use environment

- Usability
- Target population
- Diagnostic application

Scientific peer-reviewed literature input, such as search terms, methodology and inclusion/exclusion criteria, should be documented in a protocol. The results of the literature search—including the literature obtained, data retrieved and analysis—should be included in a report. The literature obtained should be statistically sound and support the device's claims. Results and their objective evaluation should then be reported in the Clinical Performance Report (CPR).



Published experience gained by routine diagnostic testing

All relevant publicly available data can be used as a source to demonstrate the clinical performance of an IVD device.

Among these:

- Reports or publicly available performance data
- Expert documents, clinical practice guidelines, consensus statements
- Data from proficiency testing or External Quality Assurance (EQA) schemes
- Data from post-market surveillance

- Customer testing
- Data from user accreditation
- Data from comparative studies

The approach to using this source of clinical performance must be stated in the PEP. Collected data and their objective evaluation should be reported in the CPR.

Other sources of clinical performance data

As already stated, the IVDR provides that: “Clinical performance studies shall be performed [...]”; however, for legacy devices that have been on the market for a few years, other data sources could be a suitable way to demonstrate clinical performance.

“Clinical performance studies conducted under the In Vitro Diagnostic Directive (IVDD) should be considered as ‘other sources of clinical performance data’ per Annex XIII 1.2.3, as they wouldn’t meet the requirements of Annex XIII 2.3,” as stated in Medical Device Coordination Group (MDCG) 2022-2.

Based on this assumption, manufacturers could consider:

- Historical clinical studies (that do not qualify as clinical performance studies under IVDR)
- Data from internal testing, e.g., design changes, investigations
- Testing of clinical specimens (performed by the manufacturer or other entities, not in the public domain)
- Data from post-market activities

Manufacturers should gather and assess all relevant clinical evidence to highlight both the clinical risks and benefits of the device. Data quality and completeness assessment are essential to identify any potential gaps.

When reviewing old or IVDD clinical studies, consider:

- Current intended use of the device
- Current State of the Art (SoTA)
- Design changes and use of any previous generations of the device
- Changes in performance claims, specimen types and device function

Manufacturers could consider the following questions:

- Does the IVDD clinical study cover all specimen types stated in the IVDR intended use?
- Was the clinical study carried out by the appropriate intended user in the appropriate intended use environment?
- Were the specimens taken from the appropriate population, representative of the European population?

If any of these answers are no, then the supporting data is likely insufficient to demonstrate the device’s claims. The manufacturer could be required to conduct a CPS or introduce limitations on the device’s use, such as specifying the target population, sample type, etc.

PMPF and product lifecycle

The IVDR requires a Post-Market Performance Follow-up (PMPF) to ensure that an IVD maintains its safety, performance and clinical evidence throughout its expected lifetime. The benefit-risk ratio must remain acceptable. Through a PMPF, manufacturers can proactively collect and evaluate device performance and scientific data within its intended purpose in a real environment by the intended user. Data that could be collected and assessed include:

- State of the Art updates
- End-user feedback
- Complaints
- Published research/studies
- New guidelines and harmonized standards

PMPF data should be reviewed regularly to assess its impact on risks and clinical benefits and determine whether updates to the performance evaluation report (PER) are needed. This information can also help guide future device developments, such as:

- Expanding the intended purpose
- Changing performance claims
- Adding new sample types

A PMPF is particularly valuable when a device is used to aid in diagnosing rare analytes or conditions, where obtaining sufficient samples to demonstrate clinical performance is challenging. A well-planned PMPF can support the future extension of claims or the inclusion of additional sample types.





Conclusion

To place IVD devices on the European Union market, manufacturers must collect sufficient clinical evidence to demonstrate the device's effectiveness and safety in relation to its intended purpose. Devices classified as higher risk (Classes B–D) require conformity assessment and surveillance conducted by a Notified Body. Notified bodies also oversee sterile Class A conformity assessments.

The level of clinical performance evidence required is directly related to the device's risk class and intended purpose. As discussed, different sources of clinical performance data may be used based on the device's characteristics. The statistical relevance of clinical performance parameters must also be carefully assessed.

Clinical performance must be clearly documented in a Clinical Performance Report (CPR), ensuring that all claims are supported with sufficient and consistent data.

Reference and guidance

Several reference documents and guidance materials provide detailed information on demonstrating clinical performance under the IVDR. Key references include:

Regulatory framework:

- Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)
- Commission Implementing Regulation (EU) 2022/1107, establishing common specifications for certain Class D IVDs

Guidance documents:

- MDCG 2022-2 – Guidance on general principles of clinical evidence for IVDs
- MDCG 2022-8 – Application of IVDR requirements to legacy devices and devices placed on the market before May 26, 2022, under Directive 98/79/EC

International standards:

- ISO 13485:2016 – Quality management systems for medical devices
- ISO 14971:2019 – Application of risk management to medical devices
- ISO 20916:2024 – Good study practice for clinical performance studies using human specimens
- ISO 14155:2020 – Good clinical practice for medical device investigations

International guidance:

- IMDRF (International Medical Device Regulators Forum) – www.imdrf.org

These resources provide essential guidance on clinical performance evaluation, ensuring compliance with IVDR requirements.

Disclaimer! Check Your Situation

SGS and the author of this white paper have checked with believed to be reliable sources in their efforts to provide complete information that is generally in accordance with European Union regulations and industry standards at the time of publication. Still, readers are advised to recheck their specific situation against the law and, when needed, seek legal or regulatory advice from professionals with relevant expertise and licensure.

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