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A RAPS Publication

Establishing and maintaining the right level of clinical evidence under the EU IVDR

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In the EU, safety and effectiveness must be demonstrated for in vitro diagnostic medical devices before they can be made available on the regional market. As demonstrated by comparing the clinical evidence with the current state of the art, devices must maintain a favorable benefit-risk ratio throughout the product lifecycle. Risk management, documentation of the state of the art, performance evaluation, and postmarket performance follow-up are continuous processes that manufacturers must carry out until product obsolescence. This article describes the steps needed to conclude that the device has a favorable benefit-risk ratio and how this conclusion should be continuously re-evaluated.

Keywords – clinical evidence, EU IVDR, in vitro diagnostic medical device, performance evaluation, postmarket performance follow-up

Introduction

The EU In Vitro Diagnostic Medical Devices Regulation (EU IVDR) requires manufacturers of in vitro diagnostic devices (IVDs) to demonstrate safety and effectiveness in an absolute manner and not by showing evidence of substantial equivalence with a predicate device that may exist on the EU market.[1] This is an important difference from the US Food and Drug Administration's (FDA's) 510(k) premarket review route, where the benefit-risk profile of the new device is determined in the context of a comparison with the benefit-risk profile of a predicate device. In the EU, safety and effectiveness must be established for each device and continuously confirmed throughout the product lifecycle by demonstrating a favorable benefit-risk ratio for the device. The EU IVDR stipulates that the clinical benefit and safety of a device must be evaluated based on the clinical evidence (scientific validity, analytical performance, and clinical performance) that is available for the device. It does not, however, prescribe in detail how clinical evidence must be established or what the required strength, robustness, and quality of the evidence should be for specific types of devices. It is up to the manufacturer to specify and justify the level of evidence required to demonstrate safety and effectiveness.

This article describes how the General Safety and Performance Requirements in Annex 1 of the EU IVDR[1] link clinical evidence of an IVD to risk management and state of the art. It explains how the required amount and quality of clinical evidence is proportional to device risk and risk classification, and how each element of clinical evidence (scientific validity, analytical performance and clinical performance) can be approached to satisfy regulators' expectations. A two-pronged approach for evaluating and documenting the state of the art for an IVD is proposed. The conclusion on the clinical evidence, established against the state of the art and in conjunction with the outcome of risk management activities, determines the benefit-risk ratio.

Clinical evidence: Linking performance evaluation with risk management and state of the art

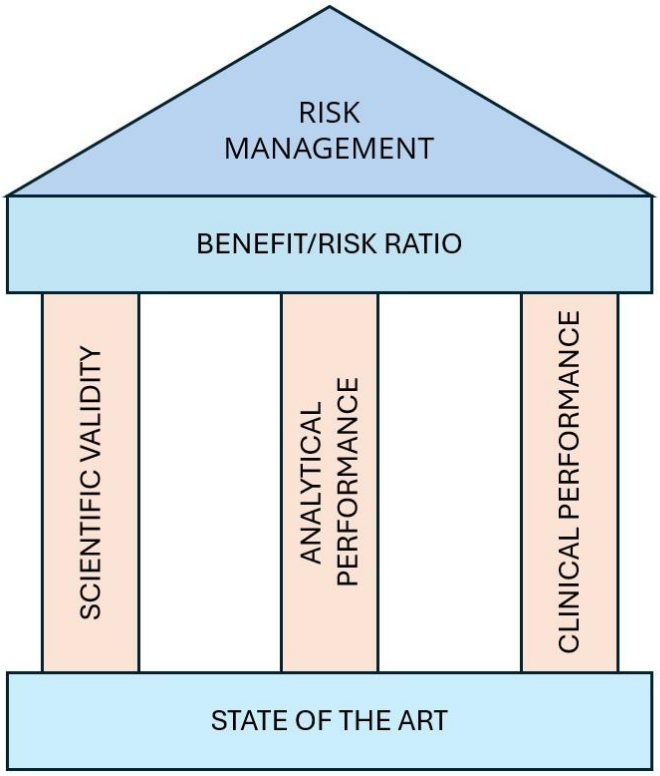
Clinical evidence refers to the results of device performance evaluation and the assessment of whether the device is safe and effective (EU IVDR Annex XIII, Part A, 1.1). The requirements for clinical evidence are effectively captured by the first clause of Annex I, which addresses the general safety and performance requirements (GSPR). The annex outlines the safety and performance requirements that apply to all IVDs unless nonapplicability can be justified. EU IVDR Annex I, 1 can be summarized as:

- The device must perform as intended by the manufacturer to fulfill its intended purpose.
- The device must be safe and effective for patients and users.
- Any device-associated risks must be acceptable when weighed against the benefit to patients.
- The device must be state-of-the-art.

Performance evaluation and clinical evidence are described in Annex XIII – Performance Evaluation (EU IVDR Annex XIII, Part A, 1.3.1). Clinical evidence comprises scientific validity, analytical performance, and clinical performance. Together, it is the amount and quality of data that allows the evaluation of the clinical benefit and safety of the device, which must be achieved in accordance with the state of the art. By performing as intended, the device is shown to be effective. To ensure that the device is also safe, risk management is applied. Through performance evaluation and risk management, the manufacturer can demonstrate that the device is both effective and safe to use and therefore has a favorable benefit-risk ratio. In summary, performance evaluation (or establishing clinical evidence) is driven by state of the art and risk management (**Figure 1)**.

Unlike FDA regulation of in vitro diagnostic medical devices, the EU IVDR does not allow an inherited claim of safety and effectiveness from a substantially equivalent predicate device on the market. Clinical evidence must be established for each device and, moreover, performance evaluation must be

Figure 1. Clinical evidence and its link with state of the art and risk management[a]



Scientific validity – The association of an analyte with a clinical condition or a physiological state (EU IVDR Article 2(38))

Analytical performance – The ability of a device to correctly detect or measure a particular analyte (EU IVDR Article 2(40))

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 accordance with the target population and intended user (EU IVDR Article 2(41))

[a]State of the art is the foundation for the three pillars of clinical evidence – scientific validity, analytical performance, and clinical performance. The pillars demonstrate the device benefit, whereas the outcome of risk management is used to evaluate the benefit-risk ratio.

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conducted continuously throughout its lifecycle (EU IVDR Annex XIII, Part A, 1.3.1 and 1.3.3). The results of performance evaluation are used to re-evaluate the benefit-risk ratio constantly. Performance evaluation, postmarket performance follow-up, and risk management constantly feed into each other until product obsolescence.

Evaluating and documenting state of the art

State of the art is a key concept of the EU IVDR and is cited 20 times throughout the legislation. EU IVDR requires a description of the state of the art as part of the device's performance evaluation plan within its technical documentation, again requiring that establishing clinical evidence must be done in relation to the current state of the art (EU IVDR Annex XIII, Part A, 1.1). State of the art is not defined within the EU IVDR, but both the medical device risk management standard ISO 14971:2019[2] and Medical Device Coordination Group (MDCG) Guidance 2022-2[3] provide clear descriptions of this concept; "the state of the art embodies what is currently and generally accepted as good practice in technology and medicine. The state of the art does not necessarily imply the

most technologically advanced solution."[3] According to this understanding of state of the art, as technology progresses, a device that is state-of-the-art today will not remain so forever. The EU IVDR requirement that IVDs be state-of-the-art implies that good technologic and medical practices must be monitored to ensure the product continuously fulfills the requirement.

When developing a new product, it is recommended to establish the state of the art early on as it drives specific product or user requirements. There is no guidance on how to evaluate and document the state of the art, but the following two-pronged approach has proven to be well-accepted by notified bodies:

- **Clinical practice –** What is the current clinical practice for the detection of a clinical condition (which analyte(s), which technology, which device(s))? This evaluation is preferably done by medical experts.
- **Performance specifications –** What is the expected performance of the device? In other words, what would be the relevant performance acceptance criteria for the device?

Sources providing information about current clinical practice include the European Centre for Disease Prevention and Control, US Centers for Disease Control and Prevention, the World Health Organization (WHO), national health authority guidelines, and international associations for specific diseases. Sources of performance specifications include common specifications or vertical standards (specific to device type), published performance characteristics or specifications (such as FDA and WHO reports), or literature sources describing the performance of current similar CE-marked devices.

The right level of clinical evidence

Demonstration of clinical evidence is proportionate to device risks and risk classification

It is the choice of the manufacturer as to how clinical evidence is established for their device. Manufacturers justify their approach as part of the technical documentation (EU IVDR, Annex XIII, Part A, 1.3.2). The exception to this rule is when common specifications (CS) apply to the device. The CS are a set of technical and/or clinical requirements, in the absence of a satisfying standard, that provide a means of complying with the legal obligations applicable to specific device types (EU IVDR Article 2(74)), which are described in Regulation (EU) 2022/1107.[4] Manufacturers must demonstrate conformity with the CS or ensure a level of safety and performance that is at least equivalent. In all other cases, it is up to the manufacturer to determine and justify the right level of clinical evidence to allow for the evaluation of the clinical benefit and safety of each device.

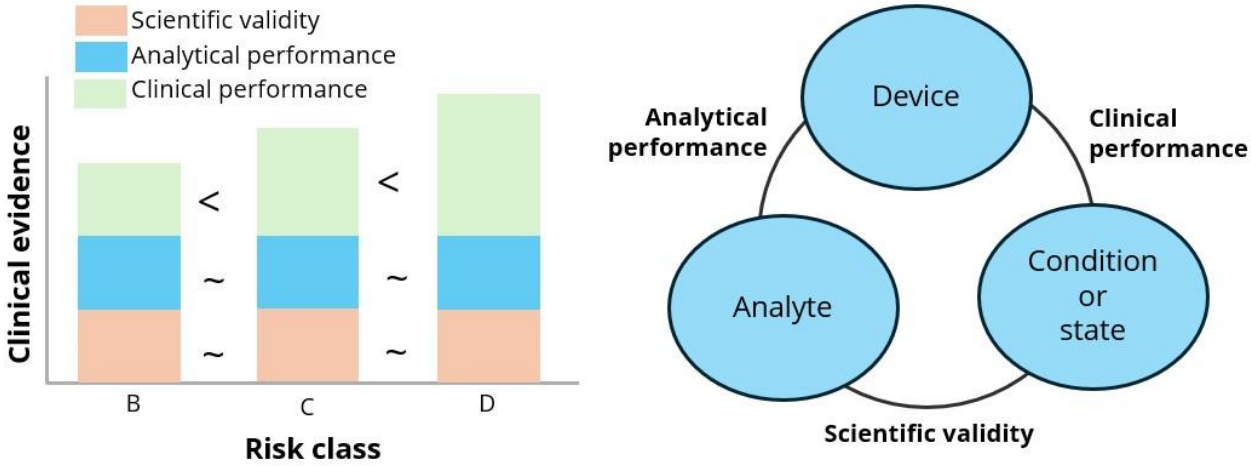
As previously mentioned, the appropriate level of clinical evidence is connected to the device risks, which are determined by the device characteristics, and the

risk class (A, B, C, or D), which is dependent on the impact of potential false positive or false negative results on individuals and public health. The key component of clinical evidence is clinical performance, that is, demonstrating that the device achieves its intended purpose in the hands of the intended user and in the intended use environment for the intended target patient population. MedTech Europe has proposed an almost direct alignment between the risk class and the required level of clinical performance, where the required levels of scientific validity and analytical performance remain largely consistent (**Figure 2**).[5] As a general rule of thumb, this approach can be used when planning performance evaluation or appraising historical data but must be considered on a case-by-case basis by the manufacturer.

Guidance on clinical evidence

MDCG Guidance 2022-2 on clinical evidence for IVDs provides valuable insights for manufacturers, giving concrete recommendations for specific cases.[3] For example, the guidance makes clear that establishing the clinical evidence for an accessory used together with one or several IVDs may be performed alongside the corresponding IVDs in question. While an accessory requires its own scientific validity, when the accessory does not detect an analyte, the scientific validity may be established through the scientific validity of the IVD. Clinical performance is also usually established by the combined use of the IVD and its accessory. Analytical performance, however, is usually best established separately on the level of either the IVD or the accessory since the latter can have specific characteristics such as precision, assignment of assay values and expected ranges, functional characteristics.

Figure 2. Clinical evidence in relation to device risk and analyte of interest, device, and target condition or state[a]



[a]Diagram on the left shows the proposed relationship between clinical evidence and device risk classification;[5] diagram on the right shows clinical evidence in relation to the analyte of interest, the device, and its target condition or state.

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MDCG Guidance 2022-2 also provides clarity for devices that detect analytes associated with a particular physiological status (such as inflammation) rather than a specific clinical condition. According to the guidance, if these analytes are adequately defined by scientific validity to be relevant in multiple clinical settings, separate clinical studies for each clinical setting or indication would not be expected. In such cases, the intended purpose should be framed to appropriately reflect the overall purpose of the IVD, for example, as a marker of inflammation rather than specifying the causes of inflammation.

Scientific validity

Scientific validity is a new concept under EU IVDR and is often misunderstood as a synonym for clinical utility; an irrelevant concept for EU IVDR. Although scientific validity can be demonstrated from results from proof-of-concept studies or from clinical performance studies, it is usually best approached by a systematic and structured review of scientific literature to prove the relationship (association) between the analyte and the clinical condition defined in the intended purpose of the device (EU IVDR Annex XIII, Part A, 1.2.1).[1] In the latter case, scientific validity is documented by a protocol, literature selection, assessment of retrieved literature, and a summarizing literature report. Scientific validity must be demonstrated for virtually all devices, including those detecting well-established analytes. The novelty of the analyte drives the required depth and robustness of the literature review. A new pregnancy test detecting human chorionic gonadotropin would still require scientific validity, but this well-established association can be summarized briefly by referring to the scientific validity of other devices on the market measuring the same analyte. For a test that phenotypes leukocytes to diagnose cancer, using well-established cellular markers, consensus expert opinions, and guidelines from professional associations may suffice. However, a test for the predisposition to a particular disease that detects a rather novel genetic biomarker will require an in-depth analysis of the available peer-reviewed literature. For some novel analytes, using internal data or device-related literature from the manufacturer may be necessary.

Manufacturers can choose whether to integrate their own device data. However, for most more common analytes, a broader scope of literature analysis that is not confined to the manufacturer's device performance is recommended.

Scientific validity may not be applicable to a device. While most reagents require scientific validity, nonapplicability can be justified for instruments, calibrators, and controls that are used with that reagent.

Analytical performance

Neither the EU IVDR nor the MDCG Guidance 2022-2 provide guidance on how analytical performance (nonclinical laboratory testing) must be established. There are no strict requirements to use specific ISO standards or guidelines from

the Clinical and Laboratory Standards Institute (CLSI) for specific devices. However, conformity assessment must consider the generally acknowledged state of the art and such documents, whenever available, because they represent the state of the art for performance evaluation. Compliance with harmonized standards, such as ISO 17511:2021 for metrological traceability, gives a presumption of conformity with IVDR requirements related to the topic of the standard. Analytical study designs modified from applicable standards or guidelines should be justified. Likewise, the use of surrogate (or contrived) samples may be necessary and is usually accepted if properly justified. Certain analytical performance characteristics may not be applicable to a device, for example, because they apply only to quantitative devices. In those cases, nonapplicability must be justified rather than simply omitted.

It is important to note that accessories also require demonstration of analytical performance for example by establishing their precision, the assignment of assay values and expected ranges, or other functional characteristics.

As previously mentioned, when CS for analytical performance are available for a device, using them is mandatory unless a justification can be provided that the obtained level of safety and performance is at least equivalent to the CS. When available, analytical CS represent the state of the art for analytic performance of a device. Where no CS are available, it is reasonable to assume that analytical studies that successfully passed a recent FDA premarket review can also be used for EU IVDR purposes. However, it remains important to check whether the review requires that all applicable analytical performance characteristics have been established. All study data should be critically appraised before being considered as compliant with EU IVDR.

Clinical performance

MDCG 2022-2 clarifies that demonstration of clinical performance is not always required, for example, for certain Class A devices such as nonsterile specimen receptacles, microscopy glass slides, or some general reagents and accessories that possess no critical characteristics.[3] Instruments, calibrators, and controls intended to be used with a reagent have no clinical performance characteristics of their own, and clinical performance is established as a combination of all these products. A justification is required in cases where the manufacturer deems clinical performance does not apply to its device.

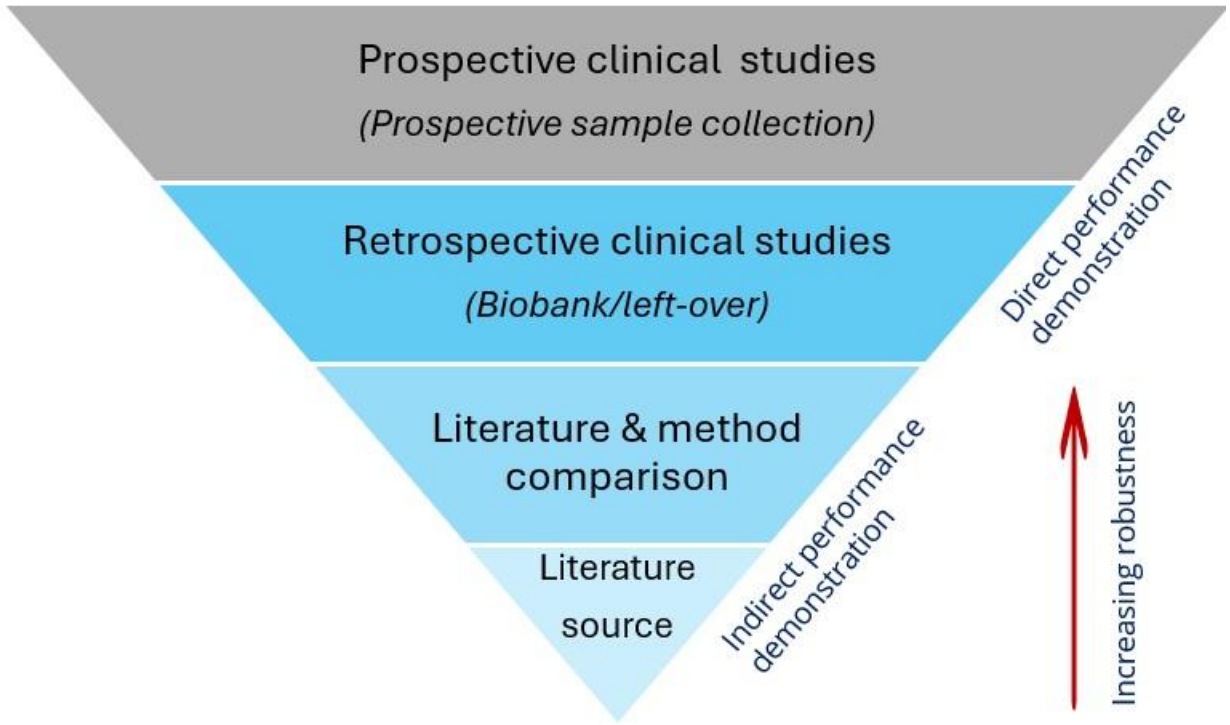
Clinical studies are not systematically required for an FDA 510(k) premarket review, although the expectation to include clinical data seems to be increasing. However, the EU IVDR stipulates that clinical performance, unless justified as not applicable to the device, must be demonstrated for each device and based on one or more of the following sources:

- Clinical performance studies,
- Scientific peer-reviewed literature,
- Data from published experience gained through routine diagnostic testing, and
- Other sources of clinical performance.

There is no specific guidance on what source should be used for each type of device. All existing clinical data should be assessed to determine the appropriate source to generate additional evidence. Clinical studies are usually necessary for devices that do not yet have a long market history in or outside the EU, but the study design may vary. The same recommendations for using applicable CLSI guidelines, standards, and CS to establish analytical performance apply to establishing clinical performance. Increased levels of detail and robustness of data (**Figure 3**) are to be expected with higher risk classifications. However, there is no fixed rule, and the appropriate approach for clinical performance evaluation should be judged on a case-by-case basis. For example, a clinical method comparison study may be appropriate for a high-risk device detecting infectious agents where a suitable comparator device is available. Conversely, there may be no option other than to directly demonstrate clinical performance when there is no commercially available comparator device, even for a lower-risk device. Further, the rationale for choosing retrospectively versus prospectively collected samples (or a combination thereof) in a clinical study may be driven by disease incidence and the availability of fresh samples. The focus of any clinical study design should be to convincingly demonstrate that the device meets its intended purpose within predefined acceptance criteria, using appropriate statistical methods. In that sense, the device's risk class may have more effect on the size and power of the study than the choice between indirect versus direct, or retrospective versus prospective studies.

It should be noted that only clinical studies performed in accordance with the EU IVDR's Annex XIII 2.3 on clinical performance are considered clinical performance studies. All clinical performance studies conducted on specimens derived from EU patients must comply with Annex XIII 2.3 requirements.[1] This does, however, not mean that clinical studies not meeting the Annex XIII 2.3 requirements cannot be considered for EU IVDR conformity assessment, but they are considered other sources of clinical performance and should not be called "clinical performance studies" for EU IVDR purposes. This includes, for example, studies conducted under the IVD Directive (preceding the EU IVDR), and studies for registration in geographies outside of the EU. Such studies remain valuable for EU IVDR, but an assessment of the quality and completeness of the data is essential to identify any potential gaps. For studies conducted under the IVD Directive, the data should be supported by published literature or data gained by routine diagnostic testing.[3]

Figure 3. **Possible means of generating clinical performance**



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The EU IVDR does not require that clinical studies be conducted within the EU or which portion of a multicontinent study should be EU-specific. It is, however, vital that the manufacturer can justify that the clinical study population is representative of the European population in relation to the analyte detected and target patient group. Literature studies are sometimes required to support that justification. Similarly, for devices detecting infectious agents, the strains that are detected in the population included in the clinical study must be representative of currently EU-circulating strains.

Usability

The EU IVDR Annex I GSPR contains several requirements related to usability, for example, in clause 5 (eliminating or reducing risks related to use error; points 5.a and 5.b), clause 13 (construction of devices and interaction with their environment; points 13.2.a, 13.2.f and 13.7), clause 19 (protection against risks posed by devices intended for self-testing or near-patient testing; points 19.1, 19.2.a and 19.2.b), and clause 20 (label and instructions for use; point 20.1.a).

While manufacturers might be able to justify the exclusion of a formal usability evaluation for certain routine IVD tests for professional laboratory use, notified bodies are increasingly interested in seeing usability evaluations of high-complexity devices provided as a part of conformity assessment. In the case of near-patient tests and self-tests, clause 19 of the GSPR is clear that usability evidence is always required (EU IVDR Annex I, 19.1 and 19.2). Studies that

validate the usability of the final device interface, when used by the intended user and in the intended use environment, should also be regarded as a source of clinical performance that can support the clinical evidence of the device.[3]

Software

Standalone software or software that is built into an IVD or supplied separately but intended to operate or influence an IVD is classified as an IVD medical device software (IVD MDSW) when it is intended to be used alone or in combination for a purpose specified in the EU IVDR definition of an IVD.[6] In such cases, the EU IVDR clinical evidence requirements also apply to IVD MDSW. This is explicitly the case for standalone IVD MDSW. MDCG 2022-2 clarifies that, for standalone IVD MDSW, scientific validity refers to the demonstrated link between the intended purpose of the software and a clinical condition or physiological state, while analytical performance refers to the software's ability to produce accurate, reliable, and precise results.[3]

The situation is somewhat different for MDSWs that are built into an IVD or supplied separately but are intended to operate or influence an IVD. In such cases, it is reasonable to claim that the scientific validity of the MDSW is derived from the IVD itself, and IVD clinical performance is established in combination with the MDSW as a system. While analytical performance will, in many cases, be established as a combination of the IVD with the MDSW as a system, the MDSW may also be responsible for a specific set of analytical performance characteristics. A notable example is a polymerase chain reaction (PCR) kit. Separately supplied software is used not only to drive and influence the PCR instrument but also to create medical information for the kit (e.g., analyte detected or not detected). In this case, the software algorithm leading to the detected or not detected result establishes the cut-off value for the PCR assay and, therefore, must be separately evaluated for analytic performance.

Using clinical evidence to evaluate the benefit-risk ratio

The benefit of an IVD to a patient is derived from its intended clinical purpose, for example, in identifying or diagnosing a disease, disease staging, or predicting disease or treatment response, among others. Performance evaluation is conducted to collect clinical evidence and confirm that the device fulfills its intended purpose. A manufacturer can use the following questions during performance evaluation:

- Is there sufficient scientific evidence that the analyte, measured or detected by the device, is associated with the disease or state for which the device is intended?
- Does the use of the device and the device's technology meet or exceed current clinical practice?
- Does the performance of the device meet or exceed that of similar or equivalent devices?

- Does the approach to gathering analytical and clinical performance evidence consider the device's risk class and the results from risk management?
- Are all performance studies designed and conducted in accordance with state-of-the-art guidance and standards and, when applicable, the CS?
- Has the usability of the device been considered?
- Do the performance studies cover all the claims of the intended purpose?
- Does each of the analytical and clinical performance characteristics meet the predefined specifications?

If the answer to all of these questions is yes, the benefit of the device is demonstrated. The second step is to make a conclusion about the overall residual risk of the device. The following questions can help a manufacturer to make this conclusion:

- Were all individual residual risks accepted?
- Has the probability of a cumulative effect of individual residual risks been considered, especially for high-severity risks that have a higher likelihood of occurring in the case of multiple simultaneous failure modes?
- Have all known risks from similar or equivalent devices been considered?

If the answer to all these questions is also yes, the device's benefit-risk ratio is favorable.

Continuous evaluation of the benefit-risk ratio

Postmarket surveillance

Conformity assessment, either through self-assessment by the manufacturer (in the case of most Class A IVDs) or through third-party review by notified bodies (all other IVDs), precedes CE-marking and making an IVD available on the EU market. While performance evaluation is an integral part of conformity assessment, the EU IVDR requires that performance evaluation also be conducted throughout the product lifecycle through postmarket surveillance (PMS). Device-specific PMS systems must actively and systematically gather, record, and analyze relevant data on the quality, performance, and safety of a device throughout its entire lifetime in order to determine, implement, and monitor preventive and corrective actions (EU IVDR Article 78.2). PMS activities typically result in the collection of data on serious incidents and side effects, batch release testing, trend reporting, and feedback and complaints. While these data are important, they do not necessarily provide all relevant information about the device's clinical evidence in a real-world setting or the impact on the benefit-risk ratio. Therefore, manufacturers cannot conclude that the retroactive collection and analysis of data through PMS is sufficient on its

own to confirm clinical benefit and favorable benefit-risk ratio throughout the lifecycle of the device. The EU IVDR also requires a proactive approach to ensure that the benefit-risk ratio can be properly assessed at any time. Although the requirements for such postmarket performance follow-up activities are risk class-dependent, they apply to all devices and have a major impact on manufacturers with devices that are placed on the EU market.

Postmarket performance follow-up

The EU IVDR explicitly states that the results from PMS activities must be used to update the performance evaluation (i.e., the clinical evidence) and benefit-risk ratio determination of the device and to improve risk management (EU IVDR Article 78.3(a) and (c)). Hence, the performance evaluation file and the risk management file for a device are live documents that must be updated with information obtained by retroactive PMS activities and through the proactive postmarket performance follow-up (PMPF) process within the PMS activities. PMPF is the continuous collection of performance evaluation data when the device is in routine use and is designed to continuously provide data. PMPF addresses uncertainties about long-term clinical performance that may impact the benefit-risk ratio in a real-world clinical setting. Consequently, PMPF requirements are described in the second part of the EU IVDR's Annex XIII, on performance evaluation, underscoring the importance of the continuity of the performance evaluation process (EU IVDR Annex XIII, Part B).

A common mistake is to narrow the PMPF process to include only PMPF studies, which are performance studies conducted to further assess, within the scope of its intended purpose, a device that already bears the CE-marking (EU IVDR Article 70.1). In general, PMPF studies are only initiated when the PMS system (including PMPF) has generated data that identifies a need for a formal performance study to readdress the adequacy of current performance evaluation data in determining the safety, performance, benefit-risk ratio, claims, and contraindications. Such data may come from the classic, reactive PMS activities described but also from proactive PMPF activities in which the manufacturer actively queries data sources and searches for information related to device performance and safety.

An important aspect of PMPF entails conducting systematic literature searches to confirm device performance or identify new risks by gathering additional clinical evidence. Other methods of obtaining data for PMPF include searching registries and vigilance databases to identify emerging risks associated with the device itself as well as similar devices, analyzing results from external quality assessment schemes to confirm clinical performance in relation to similar devices and hence, to update the state of the art, and monitoring performance of similar devices by other means to update the state of the art. PMPF also includes keeping up to date on regulatory requirements, standards, guidance, and best practices to update the state of the art and to potentially trigger device design change requests. These activities require significant resources

from a manufacturer, and there are increasing requests to reduce the PMPF burden for devices with a proven track record of safety and efficacy.

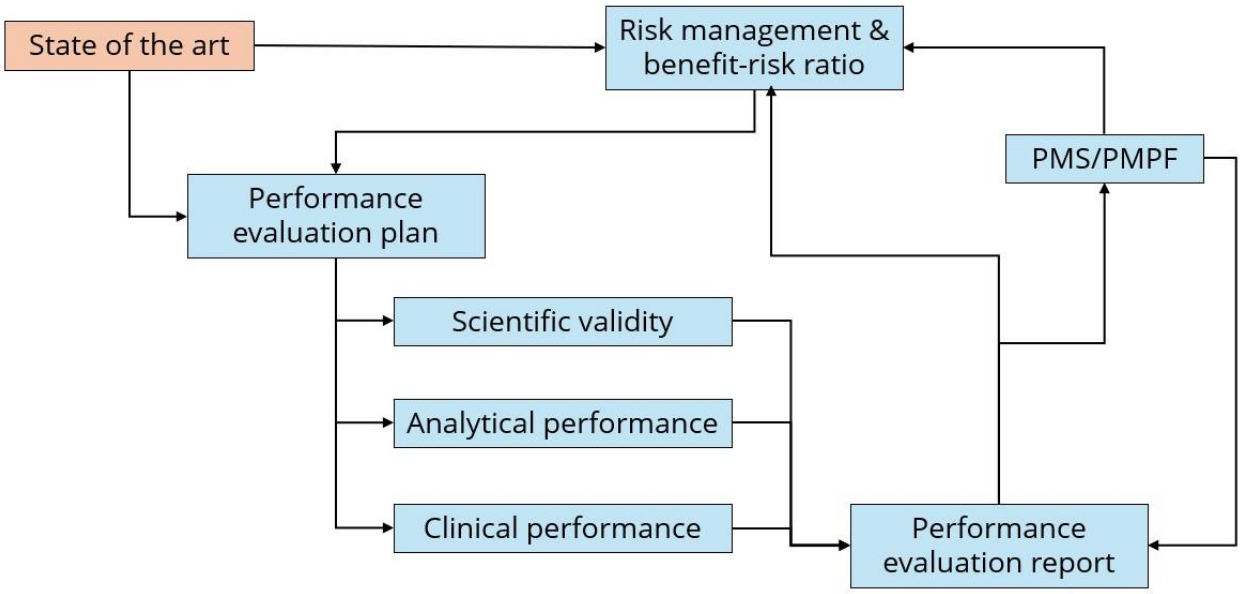
Conclusion

The EU IVDR requires that device safety and efficacy is demonstrated in an absolute manner and throughout its lifetime. **Figure 4** provides a visual summary of the process to establish and maintain clinical evidence and its relationship with risk management.

A description of the current state of the art provides important input elements for both risk management and performance evaluation during the device design and development process. Documenting the state of the art helps to define specific product and user requirements while also providing important considerations for risk management, where mitigating measures must be verified during performance evaluation. The device's performance evaluation plan must address the three pillars of clinical evidence (scientific validity, analytical performance, and clinical performance), and must do so in accordance with the current state of the art. Thus, state of the art feeds into risk management and performance evaluation (Figure 4).

Full demonstration of clinical evidence is required for all devices unless nonapplicability can be justified for certain devices. The EU IVDR does not prescribe how a manufacturer must establish clinical evidence for a device, nor does it specify what level of clinical evidence is adequate for a given device –

Figure 4. Establishing and maintaining clinical evidence under the EU IVDR



PMPF, postmarket performance follow-up; **PMS,** postmarket surveillance.

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except for devices for which CS are available. It is nonetheless clear from the first clause of the GSPR and the description of clinical evidence within the EU IVDR that state of the art and risk management are key drivers behind clinical evidence requirements and, therefore, also drivers of the demonstration of safety and effectiveness. When planning device performance evaluation, a manufacturer must consider the device risks and risk class, particularly when it comes to the demonstration of clinical performance. However, there are no fixed rules. The extent to which scientific validity must be demonstrated depends on the novelty of the analyte. Analytical and clinical performance study designs must consider state-of-the-art guidances, standards and harmonized standards to demonstrate that the device can achieve its intended purpose. Deviations or modifications from such guidance or standards should be duly justified. Generally speaking, expectations for analytical study designs are similar between the FDA and in the EU, but a critical appraisal of data generated for FDA purposes is highly recommended. Clinical studies are not necessarily conducted within the EU and must not necessarily generate direct performance data. However, they must generate data that is applicable to the European population and the robustness of the study design must reflect the device risk class.

The clinical evidence that results from the performance evaluation and is documented in the performance evaluation report is used to formulate a conclusion on the device's safety and effectiveness – that is, the benefit-risk ratio – within the risk management report (Figure 4). After a favorable assessment of this conclusion, either by self-assessment or by a notified body, the manufacturer can proceed to CE-marking and make the device available on the EU market. At the same time, the result from performance evaluation also serves to provide performance indicators for retroactive PMS and proactive PMPF activities, which must be conducted continuously throughout the postmarket lifetime of the device (Figure 4). Especially the EU IVDR PMPF requirements are considered burdensome by manufacturers, compared with other geographies' postmarket requirements.

The data obtained through PMS/PMF activities ensure that the device's performance evaluation report and risk management file can be updated continuously to confirm the device's safety and performance and state of the art and ensure continued acceptability of the clinical evidence and benefit-risk ratio.

Abbreviations

CS, common specifications; **EQAS,** external quality assessment schemes; **EU IVDR,** EU In Vitro Diagnostic Medical Devices Regulation; **GSPR,** General Safety and Performance Requirements; **hCG,** human chorionic gonadotropin; **IVD,** in vitro diagnostic medical device; **MDCG,** Medical Device Coordination Group; **MDSW,** medical device software; **PCR,** polymerase chain reaction; **PMPF,** postmarket performance follow-up; **PMS,** postmarket surveillance

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Citation Bogaert P. Establishing and maintaining the right level of clinical evidence under the EU IVDR. Regulatory Focus. Published online 21 March 2025. https://www.raps.org/News-and-Articles/News-Articles/2025/3/Establishing-and-maintaining-the-right-level-of-cl

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