Performance evaluation under IVDR

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BSI Medical Device White Paper Series

By Royal Charter

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1. Introduction

Performance evaluation is a critical part of verification and validation of product performance that is recorded in the supporting technical documentation required to place an in vitro diagnostic device (IVD) on the EU market. The requirements for performance evaluation are described within Chapter VI of the Regulation on in vitro diagnostic medical devices (EU 2017/746) (IVDR) and supported by Annexes I, II, III and XIII. Like never before, the Regulation clearly states the required clinical evidence to support verification and validation of the IVD to support its intended purpose. This white paper describes the purpose of performance evaluation, the nature of the data required to meet the requirements of clinical evidence and describes how manufacturers can meet those requirements. While this paper offers guidance, it should not be considered as a replacement for reading the full requirements of the Regulation and any issued guidance (MDCG). It is the manufacturer's responsibility to ensure full compliance with the Regulation.

Since the publication of the In Vitro Diagnostic Directive 98/79/EC (IVDD) in 1998, manufacturers of IVDs have been clear in their understanding of what body of evidence was required to support the certification of their device for the EU. The IVDD describes analytical and clinical performance characteristics in Annex I Part A Section 3 and for high-risk devices such as Annex II List A IVDs, further requirements are defined in the associated common technical specifications, depending on the specific assay. However, where the IVDD and IVDR differ, is in the further description of each of the performance characteristics to guide the manufacturer on the expectations when performing conformity assessment of the technical documentation. Prior to the publication of IVDR, the Global Harmonization Task Force (GHTF) (now superseded by the International Medical Device Regulators Forum) sought to publish further guidance on performance evaluation, defining terms such as scientific validity and clinical evidence.

Much of those publications are aligned with the IVDR and provide further guidance on the performance evaluation requirements. Furthermore, manufacturers are directed to supporting ISO standards and international guidance within BS ISO 16142-2:2017, *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 2: General essential principles and additional specific essential principles for all IVD medical devices and guidance on the selection of standards*, which ties together essential principles of IVDs with technical direction on study design to ensure some level of conformity across many device types.

2. What is performance evaluation?

Performance evaluation is defined in Article 2 of IVDR as 'an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device'. Therefore, the Regulation is describing the evaluation of three distinct sets of performance characteristics as they relate to its intended purpose. The critical point here is that the intended purpose must meet the elements listed in Annex I 20.4.1, and the classification has to be appropriate based on the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate (Annex II 1.1(c)(iii)). The manufacturer needs to consider all aspects of the intended purpose statement when determining the approach for performance evaluation in addition to the requirements of the Regulation as illustrated in Figure 1.

Understanding how to classify your device can depend on the disorder or condition your device is intended to diagnose as the manufacturer has to understand the risk to the patient or public health as a whole through misdiagnosis or misuse. This is a significant change from IVDD as the Directive defined classification by condition name, based on what was perceived as a high-risk device at that time. IVDR does not make that distinction other than for blood grouping reagents in Annex VIII. This has led to the majority of IVDs that were placed on the market after 1998 being classed as self-declared (which presents other challenges as discussed later in this paper). MDCG 2020-16 *Guidance on classification rules for in vitro diagnostic medical devices under Regulation (EU) 2017/746* provides further classification guidance for IVDR and specific examples for reference.

Figure 1. Intended purpose requirements.
Note: The terms intended use and intended purpose are interchangeable under IVDR.

Analyte

- Provide evidence of association between analyte & condition in scientific validity report
- Verify the analytical performance
- Validate the clinical performance

Function

- Confirm function in scientific validity report
- Provide validation evidence in clinical performance report

Condition

- Provide evidence of association between analyte & condition in scientific validity report and clinical performance report

Automated?

- Validate the device in combination with automated system if applicable

Qualitative/ quantitative

- Provide validation data for measuring range/ cut-off as approporiate

Specimen type

- Provide evidence that specimen type is appropriate in scientific vailidity report, clinical performance report or as part of the State of the Art assessment
- Verify that the device can detect the analyte in specimens of this type
- Validate the testing of specimens following storage

Testing population

- Provide evidence of general population or specific patient groups that can be tested with the device ('state of the art in medicine') either in scientific validity report or as part of clinical performance

Intended user

- Provide clinical evidence of device validation by the Intended User e.g. Professional near-patient and/or lay user

Clinical evidence is defined in Article 2 of the Regulation as 'clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer'. So, the definition of clinical evidence suggests a risk-based approach to defining the clinical benefits, and ultimately the requirements for the device, determined by the intended purpose, classification and risk management. Therefore, the manufacturer would consider the performance evaluation requirements for a Class A specimen receptacle very differently to a Class D HIV assay. A fully detailed understanding of intended purpose and clinical use of the device is required at an early stage of product development in order to correctly define design inputs as they relate to performance evaluation.

Performance evaluation should be a part of the quality management system for an IVD. BS EN ISO 13485:2016 describes the requirements to define performance in design inputs as part of the design and development process and conducts performance evaluation as part of design validation in accordance with applicable regulatory requirements. Therefore, the concept of conducting performance evaluation is not new to IVD manufacturers, but they are required to adapt to the new elements now included within IVDR in order to place their device on the market in the EU. Figure 2 illustrates how performance evaluation requirements should be defined very early in the design of the device and how each step of the process should inform how the next step is approached.

Figure 2. Performance evaluation process. PEP, performance evaluation plan; PER, performance evaluation report; PMPF, post-market performance follow-up

Design inputs

- Define the Intended Purpose
- Write the performance evaluation requirements into the Design inputs

PEP

- Define the approach for all aspects of Performance Evaluation
- Describe the studies to be conducted or reappraised

Scientific validity

- Appraise peer-reviewed literature demonstrating associate of the analyte with the condition OR:
- Provide evidence from the studies

Analytical performance

- Conduct studies to meet the requirements of the regulation

Clinical performance

- Gather study data and/or literature to demonstrate clinical performance of the device suitable to its Intended Purpose

PER

- Summarize all clinical evidence
- Conclude risk benefits of the device
- Describe PMPF activities if required

PMPF

- Conduct activities throughout the device lifecycle to confirm performance
- Update performance evaluation documents as necessary

3. Performance evaluation plan

Although the concept and requirements of performance evaluation have not really changed over 20 years, the required technical documentation has changed radically both in terms of content and amount required in the IVDR compared to the IVDD. The contents of two new IVDR documents are explicitly described in Annex XIII: the performance evaluation plan (PEP) and the performance evaluation report (PER). The PEP provides the manufacturer the opportunity to take the design inputs for performance and safety together with risk management outputs and align them to the IVDR requirements described in Annex I, Sections 1–9. Sections 1–9 encompass safety, risk, performance (i.e. scientific validity, analytical and clinical performance) and stability (lifetime, transport/storage and in-use) as illustrated in Figure 3.

By aligning design inputs with IVDR requirements, the manufacturer can then plan how to generate the appropriate data required to support each performance characteristic. Although the requirements for performance and stability may seem obvious, clinical evidence data to support safety and risk can be less so. This is where the manufacturer has to think outside their own testing environment and bring in real-world experience of the device (or similar related devices), which can be used as additional clinical evidence to support the safety and benefit-risk ratio of the device.

This is discussed further in the following clinical performance section. The requirements for the PEP include an overview of the design phases within which each data set will be generated, so there is an expectation of an integration of this document with the design and development process.

For legacy devices (those already on the market under IVDD), this may present a challenge for some manufacturers. A PEP is still required, but the approach to gathering clinical evidence will differ from that for new devices. It is expected that manufacturers re-appraise the clinical evidence they hold for a device to determine its suitability under IVDR. This may mean that previous clinical studies performed for the device do not meet Annex XIII/BS ISO 20916:2019 requirements (see Clinical performance below), or additional data has been gathered since placing the device on the market under IVDD. Furthermore, the intended purpose under IVDR may have subtlety changed compared to IVDD, thereby impacting the clinical evidence required. Manufacturers should describe how performance evaluation data will be reviewed in the PEP and determine if there are any gaps to be filled to meet IVDR requirements.

Figure 3. Summary of Annex I, Sections 1–9 requirements for performance evaluation.

4. Scientific validity

Scientific validity was defined for IVDs in 2012 by GHTF prior to publication of the IVDR. The definition in Article 2 of the Regulation describes scientific validity as 'the association of an analyte with a clinical condition or a physiological state'. Annex XIII expands on this definition and guides the manufacturer on sources of evidence that can be used to meet the requirement. For well-established assays, the description of clinical guidelines or published literature will suffice, whereas for newly developed assays, where published evidence is limited, the manufacturer will need to provide their own evidence for scientific validity such as proof-of-concept studies or clinical performance studies. The literature or data has to be summarized in the scientific validity report (SVR) as it pertains to the specific claims stated by the manufacturer in the intended purpose of the device. That understanding of the 'specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate' is critical, as are any limitations on which conditions the device can be used to diagnose. The Regulation does not dictate the format of the SVR, but it needs to make clear which clinical condition(s) the analyte is associated with and which of those are claims for the device itself. Other analytical performance characteristics can play a part here (i.e. measuring range or interfering substances). As described in GHTF/SG5/N7:2012, *Clinical evidence for IVD medical devices — Scientific validity and performance evaluation*, the evidence for scientific validity has to be appraised for its relevance and quality, with references, justifications and conclusions, which provides some guidance on the layout of the report.

Certain Class A devices or controls and calibrators may not require scientific validity to support clinical evidence. Where these devices do not perform the assay itself, the PEP will need to describe that although scientific validity is not applicable for this type of device, scientific validity from the associated assay is valid. So, for manufacturers that only place controls or calibrators on the market, for example, they will need to provide an SVR describing the association of the analyte for the assay(s) they are supporting.

Figure 4. SVR considerations

Analyte claims

- All analytes must be listed with distinct literature or data to support the association with the listed conditions

Condition claims

- All conditions must be specified with appropriate measuring ranges/cut-offs for clinical diagnosis
- Justification must be provided in the scientific validity report for broad or generic conditions described in the intended purpose
- Reference international clinical guidance when describing the clinical condition

Testing population claims

- Describe any limitations on the testing population such as patients outside specified age range or patients with particular conditions
- Provide literature or device data demonstrating suitability for testing on these patient types

5. Analytical performance

Analytical performance is not a new concept for IVDs, having been described in the IVDD since 1998. Many of the same analytical performance characteristics are present in both IVDD and IVDR, but IVDR seeks to expand on what nature of data should be provided. Section 9.1 of Annex I describes the analytical performance requirements, but as all scenarios of device type and intended purpose cannot be anticipated, the onus is on the manufacturer to provide a rationale for any characteristics that are not applicable to their device. This is most evident when determining analytical performance requirements for qualitative as opposed to quantitative devices. BS ISO 16142-2:2017 directs the manufacturer to international guidance documents, which are most appropriate for aiding in study design.

The requirements for analytical performance do not differ for Class B, C and D devices, but again, an assessment will be required on what analytical performance characteristics, if any, are appropriate for Class A devices. BS EN ISO 18113-3:2009, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 3: In vitro diagnostic instruments for professional use*, does provide some guidance on performance characteristics that should be described in the labelling for instruments. Testing for compliance with common technical specifications (to be known as common specifications once published as an implementing act for IVDR) for Class D devices can be documented under analytical performance and clinical performance, as appropriate. Figure 5 lists typical studies that would be considered analytical performance.

The IVDR does not provide guidance on the content and layout of the analytical performance report (APR), other than to state in Annex XIII 1.2.2 that 'the manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters described in point (a) of Section 9.1 of Annex I, unless any omission can be justified as not applicable. As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies'. Therefore as a minimum, the APR will need to link back to the PEP, describe the studies performed in sufficient detail, provide an explanation of why certain performance characteristics are not applicable and support the claims being made in the instructions for use (IFU).

Figure 5. Analytical performance requirements for different IVD types

- Specimen type, specimen storage/handling specimen transport,
- Trueness vs reference method/material, total analytical error, repeatability & reproducibility, senstitivity
- Interfering substance & cross-reactivity
- Measuring range (LoB, LoD, LoQ), linearity, cut-off

- Metrological traceability
- Batch-to-batch Homogeneity

- Carryover
- Instrument-to-instrument precision

6. Clinical performance

Manufacturers may have traditionally thought that clinical studies provide the sole clinical evidence for the device. The IVDR states that clinical performance studies may not be necessary to support the intended purpose of the device (Annex XIII 1.2.3), and other options include scientific peer-reviewed literature or published experience gained by routine diagnostic testing. The necessity for clinical performance studies is dependent on the intended purpose and the extent of analytical performance conducted for the device. So far in this paper, the performance evaluation requirements for IVDs are distinct from those described for clinical evaluation of medical devices, but here is where the two regulations overlap and some parallels can be drawn from the available guidance and experience of clinical evaluation under MDD/MDR. Annex XIII 1.2.3 of IVDR describes multiple options for gathering clinical performance data to complete the clinical evidence of the device. This is nothing new for medical device manufacturers as the MEDDEV 2.7/1 guidance on clinical evaluation (for medical devices under MDD/AIMDD) describes how to plan, identify, appraise and ultimately report clinical data for the device. Readers will recognize parallels between the clinical evaluation report requirements and the PER. Whereas, in the past under IVDD, manufacturers will have conducted a clinical study to validate their device, which may not be enough to support the safety, risk and performance requirements stated in Annex I and outlined in the PEP.

In order to determine if clinical performance studies are required for the device, a deep understanding of the intended purpose and clinical use is required. For devices measuring analytes that are associated with a clinical condition that have medical decision points, clinical performance data and a corresponding clinical performance report (CPR) are required. Typical clinical performance data could be diagnostic sensitivity and specificity, area under the curve, negative predictive value and positive predictive value. For devices measuring analytes without clear medical decision points or for devices measuring analytes that are not (yet) associated with a clinical condition, clinical performance may be defined as correlation with a physiological state, or a justification for omission of clinical performance studies may be considered. Typical data presented would be negative percent agreement and positive percent agreement.

As mentioned earlier, the Regulation does describe what nature of data may be used to support clinical performance

Figure 6. CPR requirements

Clinical performance studies

- Perform clinical studies performed by BS ISO 20916:2019 with the device
- Risk analysis and the Intended Purpose should inform the manufacturer within which environments studies should be conducted
- Near-Patient or self test validation is required

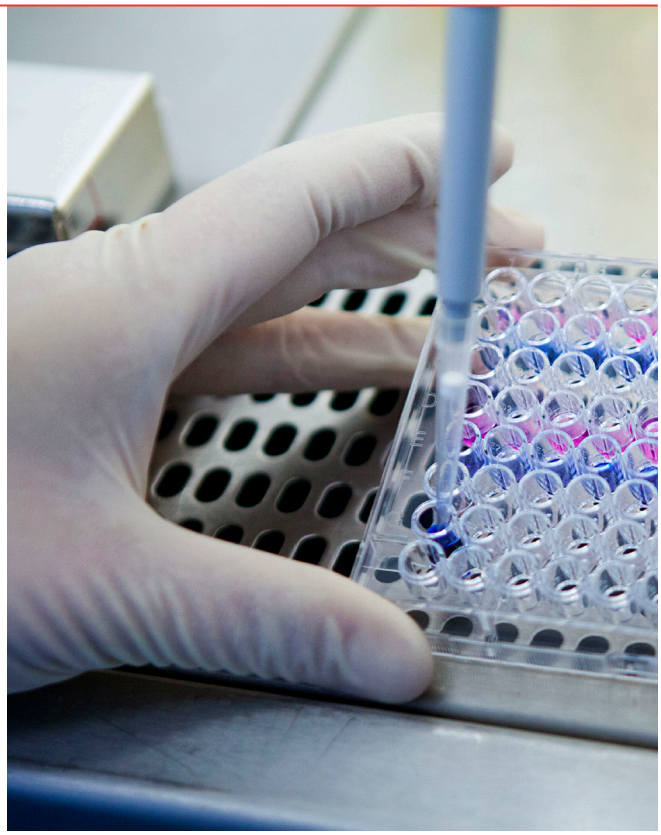
Peer-reviewed literature

- Where clinical performance studies are not necessary or appropriate for the device, clinical evidence can be gathered from literature
- Use an objective method to conduct searches on appropriate databases for your device
- Clinical texts can also be relevant to support the clinical performance of the device according to the intended purpose

Published routine diagnostic testing

- Publications outside peer-reviewed literature can be appraised to support the clinical evidence for the device
- WHO reports or data from EQAS schemes are ideal sources of device performance data

7. Clinical performance studies



The purpose of clinical performance studies is to establish or confirm aspects of device performance that cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing (see below). Clinical performance studies are described in detail in the Regulation, predominantly throughout Chapter VI and Annexes XIII and XIV. This new term is analogous to a clinical study performed in the past, but is specific to IVDR; therefore, any studies conducted prior to IVDR entry into force do not qualify as a clinical performance study. Any legacy clinical studies not specifically conducted for IVDR should be documented under 'other clinical studies' within the CPR. Studies conducted under IVDR though do have to conform to the requirements set out in the Regulation for protocols (now known as clinical performance study plans or CPSP – see Annex XIII 2.3.2), the study conduct itself and the study report (now known as the clinical performance study report or CPSR – see Annex XIII 2.3.3). The requirements for clinical performance studies are well aligned with BS ISO 20916:2019, *In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice* and good clinical practice guidelines published by other EU agencies.

Manufacturers need to consider if direct or indirect clinical performance data is required on their device. Direct performance data would comprise either prospective or retrospective clinical studies on the device itself and provides the strongest clinical evidence. Indirect performance data is derived from a comparator or standardized device, however, proving equivalence between IVDs presents more challenges than can be done for medical devices, for example and therefore unlikely to meet the requirements of the Regulation. The onus is on the manufacturer to justify why direct clinical data is not possible for their device. Similar to requirements under IVDD, clinical performance studies can be described as (Annex XIII 1.2.3):

- study using left-over samples
- study posing no risk to patients
- interventional studies or studies posing a risk to patients

The requirements for approval and conduct of these studies are clearly explained in the Regulation.

8. Scientific peer-reviewed literature

Annex XIII 1.2.3 refers to scientific peer-reviewed literature as an option to demonstrate clinical performance of the device, and the earlier section of the Regulation on scientific validity (Annex XIII 1.2) describes the requirement for documenting the literature search methodology, protocol and report of a literature review conducted to support performance evaluation. Although not written to support IVDR, some guidance can be taken from MEDDEV 2.7/1 on how to structure a literature search for medical devices. It recommends that objective, non-biased, systematic search and review methods should be used in order to identify both favourable and unfavourable data for the device. Examples are provided in the publication.

The protocol should describe the background, objective and methods for identification, selection and collection of the relevant publications to address the literature review questions. Appropriate databases should be selected pertinent to the intended purpose of the device such as PubMed or the Cochrane Library. It is recommended that manufacturers establish a clear, methodical and justified procedure for conducting any literature search to maintain unbiased reproducibility of results. Appraisal of the literature should be documented in the CPR, making clear the weighting of each publication to support the clinical evidence. Data from literature can be used to support the safety and performance claims for the device.

9. Published experience gained by routine diagnostic testing

Further clinical performance data can be gathered from routine diagnostic testing. This can take the form of published reports issued for sale or distribution to the public or any performance data that is issued publicly. Data can also be derived from real world evidence such as evaluation by competent authorities, data obtained from user accreditation (laboratory validation data), proficiency data reports/external quality assurance data (e.g. independent medical and/or laboratory associations such as WHO or IFCC) or from post launch studies (after CE marking). It is recommended that this approach is explained in the PEP and data fitting this criteria is summarized in the CPR.

10. Other sources of clinical data

Manufacturers are encouraged to gather all relevant clinical evidence in order to understand the clinical risks and benefits for the device. Where manufacturers have other data on clinical performance such as adverse event reports or testing of clinical specimens that is not in the public domain, this can be gathered under 'other clinical evidence' in the CPR. Furthermore, for legacy devices, historical clinical studies may not qualify as clinical performance studies under IVDR (i.e. not meeting Annex XIII or BS ISO 20916:2019 requirements) and so although they will not meet one of the three options for clinical performance, they can be described under 'other clinical evidence' for consideration.

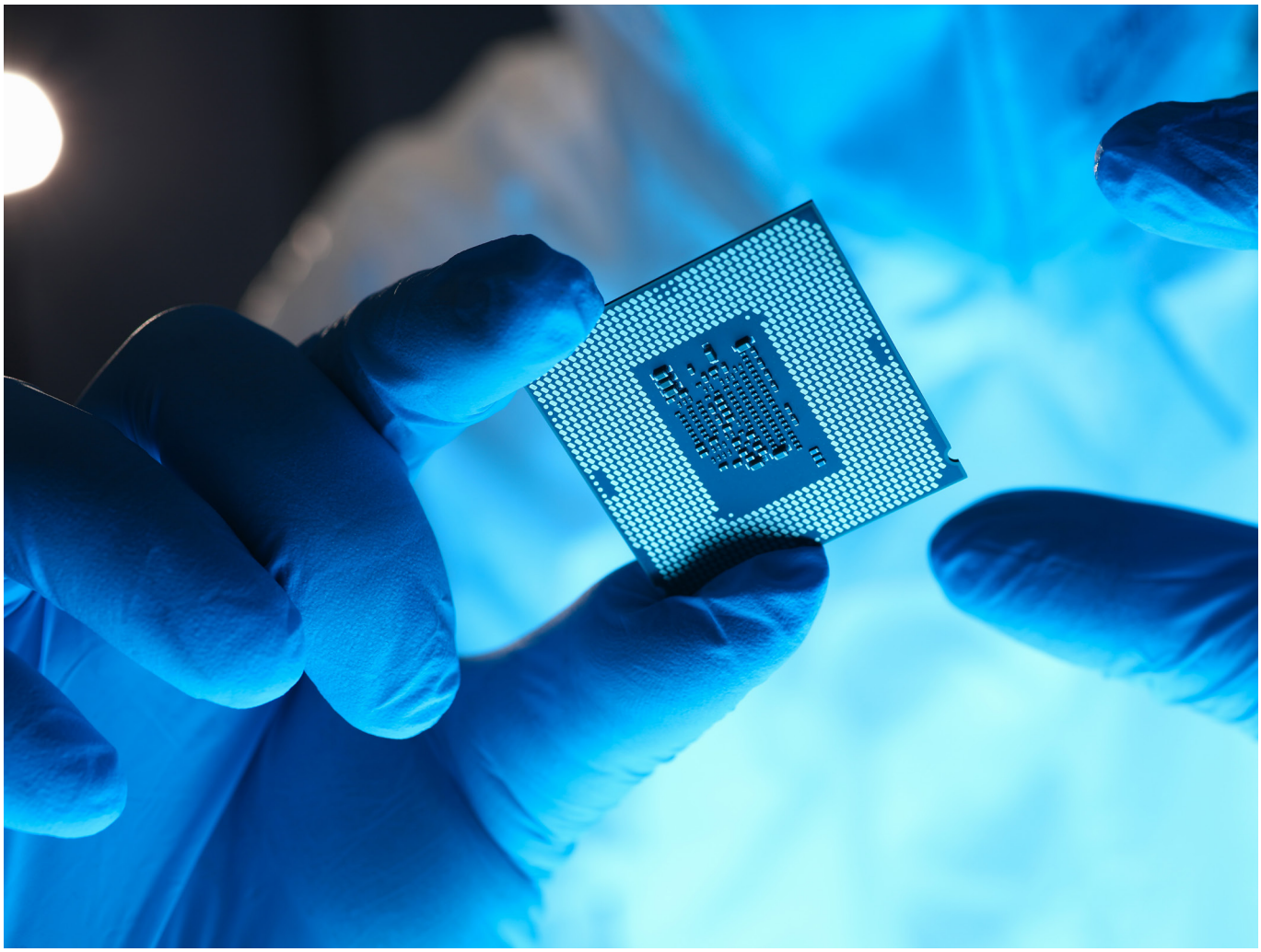
11. Clinical Performance Report

The requirement to summarize all clinical performance of the device in the CPR is stated in Annex XIII but the format and contents are not described. It is expected the manufacturer will tailor the format of the CPR to suit the required clinical performance data for the device while accounting for each of the three 'options'. Furthermore, any special characteristics of the device such as near-patient, self-test or specific clinical claims outlined in the intended purpose will be addressed in the CPR. It is recommended to have dedicated sections of the report to account for this. If the PEP has described the requirement of clinical performance data required to support safety, risk or performance, that data should be documented here and linked back to the PEP. Manufacturers are encouraged to use additional forms of data such as post-market surveillance (PMS) data or comparator product information to support the argument that the device is safe and effective. This data can also be used to demonstrate the device is state-of-the-art in medicine.

12. State-of-the-art

State-of-the-art is defined in BS EN ISO 14971:2019+A11:2021 as the 'developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience. 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'. State of the art is referenced throughout the Regulation with regards to clinical performance and safety. Ultimately, the manufacturer needs to demonstrate that state-of-the-art methods have been employed with regards to design, manufacture, performance, risk management, safety and stability.

The base argument for this is compliance with international standards and guidance documents such as those recommended in BS ISO 16142-2:2017, but the manufacturer may choose to gather evidence from other sources such as clinical guidelines or performance evaluation data to prove their device is state-of-the-art. The PEP has to describe the approach for state-of-the-art, and the conclusions need to be documented in the PER. Manufacturers should be aware that this process can ultimately determine their device is not state-of-the-art and consider if this will trigger further studies to be performed, a change to the device design or withdrawal from the market.



13. Performance evaluation report

The PER is the second performance evaluation document fully defined within the Regulation. Annex XIII 1.3.2 describes the content requirements of the PER, which serves to collate the conclusions of the SVR, APR, CPR, state-of-the-art, benefit-risk and post-market performance follow-up (PMPF; see below). This is the key document for performance evaluation because it brings all elements of clinical evidence together for the device in context with benefit-risk statements and state-of-the-art status. This document provides the opportunity for the manufacturer to discuss the device in relation to its intended purpose and risk classification. The PER is updated throughout the life cycle of the device: annually for Class C and Class D devices (as stated in Article 56), and on a regular schedule for Class A and Class B devices as appropriate (as fits with the quality certification cycle). As this document is multi-disciplinary, it is crucial that the manufacturer organizes the writing and maintenance of this document and fully integrates it into the infrastructure of the quality management system.

Figure 7. Considerations for state-of-the-art

14. Post-market performance follow-up

PMPF is defined in Part B of Annex XIII as ‘a continuous process that updates the performance evaluation’ and goes on to state ‘with the aim of confirming the safety, performance and scientific validity throughout the expected lifetime of the device, of ensuring the continued acceptability of the benefit-risk ratio and of detecting emerging risks on the basis of factual evidence’. This is a new requirement under IVDR and is analogous to the similarly termed post-market clinical follow-up in MDR. The contents of the PMPF plan are prescriptive in the Regulation, and are extensions of the activities conducted under PMS but specifically with the aim of collecting additional performance data once the device is on the market. PMPF essentially serves to continue to support the PEP/PER throughout the device’s life cycle and is particularly useful when monitoring scientific or clinical developments that can impact the performance of the device. Examples can be possible misuse, emerging strains of infectious diseases or new substances that may interfere or cross-react with the device. The typical methods employed would be monitoring customer complaints, review of scientific literature, awareness of changes to clinical guidelines, ongoing collection of published routine diagnostic testing and appraisal of comparator device labelling.

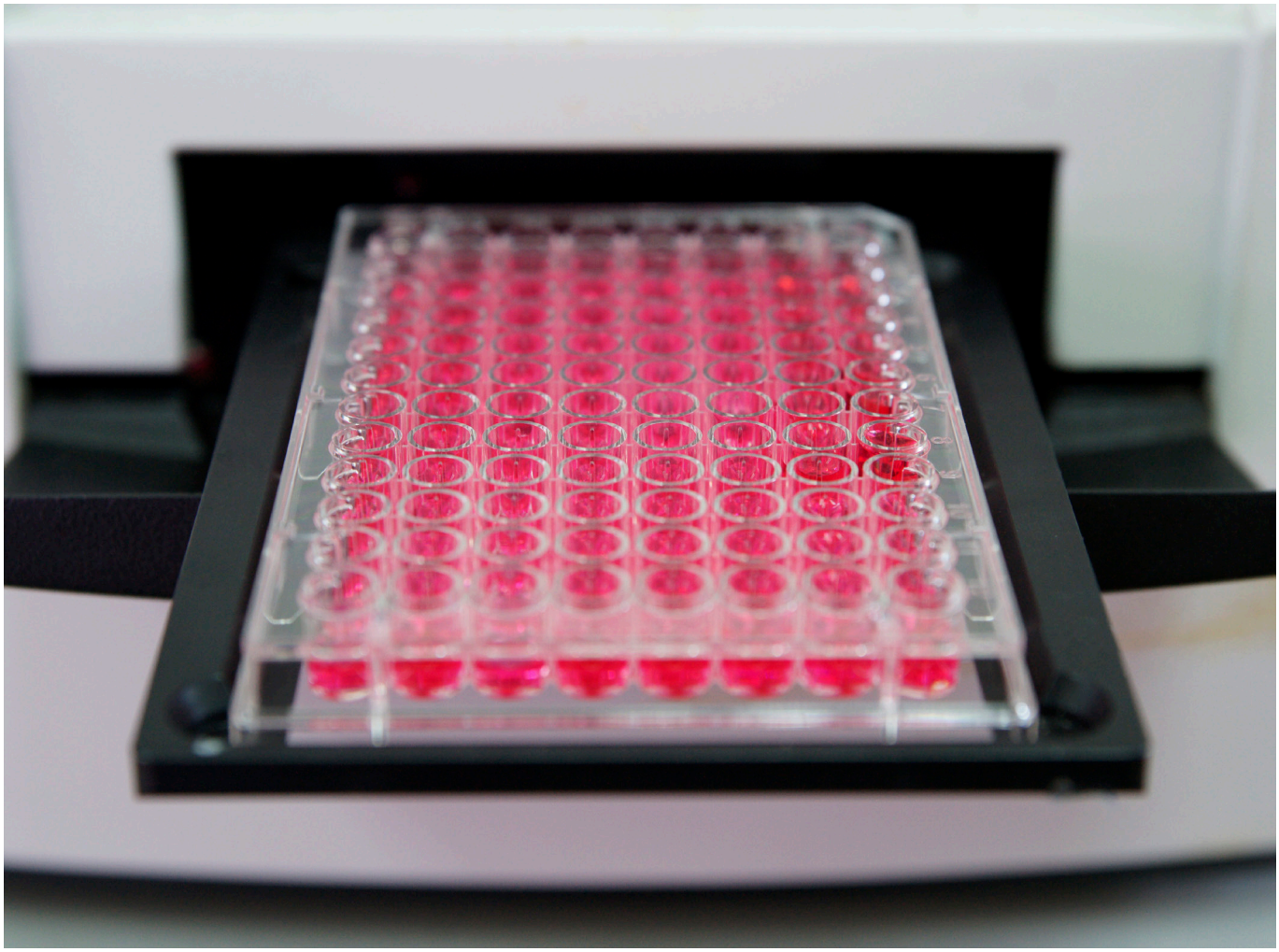
Furthermore, PMPF serves to continue to support the argument that the device is state-of-the-art until such a point it is deemed no longer suitable for the market. The Regulation does concede, however, that PMPF could not be appropriate or required for certain devices and so the manufacturer can choose not to write a PMPF Plan (i.e. if further studies are not required and other aspects are covered as part of post-market surveillance), but will need to document the rationale for lack of PMPF in the PEP. This can be the case particularly for well-established devices where the body of evidence is large and there is little change in clinical evidence. Outputs from PMPF are written in the PMPF evaluation report where it is then determined if those outputs result in:

- an update to the associated performance evaluation documentation
  a revision of the risk management reports
- a CAPA is raised
- further PMPF studies are conducted or
- all of the above

It is suggested a new PMPF evaluation report is created when each cycle of PMPF is completed to document the activities performed. If necessary, the PER should be updated with PMPF data if the need arises before the scheduled date.

15. Summary of safety and performance

The summary of safety and performance (SSP) is described in Article 29 of the Regulation and is required for Class C and Class D devices only. It is important for the manufacturer to understand that other than the labelling, this is the only other document available to the public through publication on the European Database on Medical Devices (EUDAMED). This document provides an executive summary of the safety and performance characteristics of the device, and the contents are validated by the relevant notified body against the technical documentation. The notified body is responsible for validating the SSP and uploading to EUDAMED where it is accessible by the public, other manufacturers, the competent authorities and the European Commission. Due to the requirement for translation, it is recommended that the text is kept succinct and specific, using recognized symbols and terms wherever possible. The SSP draws from the supporting technical documentation and the IFU, but also specifies the user profiles of the device. Guidance on the content of the SSCP (MDR) is available from MDCG with a similar template available soon for IVDR.



16. Specific device types

16.1 Near-patient

Near-patient devices are a new concept under IVDR. The definition of near-patient is defined in Article 2 of the Regulation as 'any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional'. Manufacturers are now required to define the near-patient environment within which their device is used and validate the use of the device in that near-patient environment (as stated in Annex I 9.4). Manufacturers again need to have that deep understanding of the intended purpose and clinical use of their device but most importantly understand the training and environment of the users.
User qualifications and training are to be considered during the risk management process to enable appropriate instructions and warnings to be provided in the IFU.

The device has to be validated in the near-patient environment and verification of the IFU as a risk control should satisfy BS EN ISO 14971:2019+A11:2021 requirements. Examples of near-patient environments could be physician offices or clinics, emergency care rooms or an emergency vehicle. Each environment presents its own challenges with regards to user training and environmental conditions. Annex II 3.1 directs the manufacturer to describe the near-patient design aspects in the technical documentation,

17. Self-testing devices

A device for self-testing is defined in Article 2 as 'any device intended by the manufacturer to be used by lay persons, including devices used for testing services offered to lay persons by means of information society services'. Self-testing devices were already regulated under IVDD and required conformity assessment by a notified body. Similarly to Annex II List A devices, self-test devices will likely have an IVDD certificate that extends beyond the IVDR date of application, giving manufacturers some breathing room. Self-test devices are not dependent on the issuance of new common specifications or the establishment of reference laboratories (see Practical advice below), but IVDR does tighten up the requirements for appropriate training or labelling for the device for these user types. Similarly to near-patient devices, manufacturers have to describe the design aspects that make them suitable as self-test devices in the technical documentation, and so they need to consider the appropriate performance evaluation approach as an output of the design and risk management process.

18. Companion diagnostics

A companion diagnostic is defined in Article 2 as 'a device which is essential for the safe and effective use of a corresponding medicinal product to: (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product'. Companion diagnostics have the same performance evaluation requirements as other IVDs, with the additional requirement of validating the device with the associated medicinal product. This ties in with the requirement to include the target patient population and associated medicinal product in the intended purpose (Annex II 1.1). Companion diagnostics are Class C as per Annex VIII and so are subject to the same performance evaluation requirements as other Class C devices and more likely to have requirements from interventional studies.

19. Controls and calibrators

Controls and calibrators fall outside some of the expected performance characteristics for assays. There is an expectation that a PEP and PER are written for these devices (or combined with their associated assay documents if in the same technical file), but a justification will need to be provided if particular performance characteristics are not applicable. Manufacturers should note any specific labelling requirements for controls and calibrators defined in Annex I that would require supporting performance data such as metrological traceability, batch-to-batch homogeneity and stability to ensure this is addressed in the performance evaluation documentation.

20. Practical advice to manufacturers

20.1 Immediate challenges

The impact of the new requirements of performance evaluation on IVDs currently on the market under IVDD cannot be underestimated. Many 'legacy' products have been on the market prior to the IVDD date of application and were accepted on the basis of demonstrated on-market safety and performance. Grandfathering of devices already on the market is not accepted under IVDR, and so each and every IVD has to meet all the performance evaluation requirements as appropriate to the device's intended purpose and risk classification. Manufacturers will no doubt be playing catch-up to gather additional clinical evidence to meet the requirements of the Regulation and could find the proposal of re-appraising data previously generated under IVDD somewhat daunting or even unnecessary. There are no exceptions in IVDR for performance evaluation without a robust justification, and so manufacturers are advised to take steps as early as possible to fill any data 'gaps' and minimize the potential for any challenges to the conformity assessment of their device.

20.2 Notified body interpretation

Guidance documents on IVDs have not yet been released to clarify additional requirements for performance evaluation. To date, manufacturers should use MDCG guidance where it exists or gained experience under IVDD to direct them on what to provide in their technical documentation. There is a risk that manufacturers and notified bodies will not interpret the performance evaluation requirements in the same way, leaving little time for gaining certification to place on the market. This may be critical for making significant changes or placing new devices on the market. It will also become important as the revised transition dates approach. Manufacturers are encouraged to submit their technical documentation as soon as possible to provide sufficient time to meet the notified body expectations.

20.3 Class D devices

The majority of Class D devices currently on the market under the IVDD are certified as Annex II List A with associated common technical specifications. It is thought once the common specifications are published, these products will not be adversely affected. However, for those devices currently Annex II List B or self-declared under IVDD, the lack of common specifications for IVDR poses a problem. Annex II List B devices have until certificate expiry to continue marketing under IVDD but self-declared devices are limited by the date of application. This issue is further complicated by the fact that critical infrastructure being missing (EU Reference Laboratories) means certification towards IVDR as a Class D is more challenging for both manufacturers and notified bodies. Manufacturers are advised to gain time while these supporting requirements are put into place by leveraging Article 110 Section 4 to ensure continuity of supply for users and patients.

Conclusion

Performance evaluation has now been intimately linked with risk management and PMS throughout the life cycle of the device in a way never seen before for IVDs. This is a response to post-market performance issues for medical devices as a whole over the last 20 years and is reflected in the parallels between the medical device and in vitro medical device regulations. Tighter controls for on-market performance have been implemented to ensure ongoing safety to both user and patient. As ever, elements of performance evaluation under the IVDR are quite prescriptive in their nature, but the Regulation also allows flexibility in its application as not all device scenarios can be described. The onus is on the manufacturer to bring together design control, risk management, performance evaluation and PMS with that deep understanding of the clinical use of the device in order to meet the mark for conformity assessment.

Manufacturers will need to adjust to this new approach of going beyond initial product validation and embracing ongoing performance evaluation monitoring throughout the device's life cycle. This will no doubt be a challenge with the additional reporting and resource that this entails.

Further Reading

- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (IVDR)
- Regulation (EU) 2022/112 Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices (IVDD)
- BS EN ISO 13485:2016, Medical devices — *Quality management systems — Requirements for regulatory purposes*
- BS EN ISO 14971:2019+A11:2021, *Medical devices — Application of risk management to medical devices*
- BS ISO 16142-2:2017, Medical devices — *Recognized essential principles of safety and performance of medical devices — Part 2: General essential principles and additional specific essential principles for all IVD medical devices and guidance on the selection of standards*
- BS EN ISO 18113-3:2009, In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 3: In vitro diagnostic instruments for professional use
- BS ISO 20916:2019, In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
- MDCG 2020-16, Guidance on Classification Rules for in vitro diagnostic medical devices under Regulation (EU) 2017/746
- MDCG 2022-2, Guidance on general principles of clinical evidence for in vitro diagnostic medical devices (IVDs)
- GHTF/SG5/N7:2012, Clinical evidence for IVD medical devices — Scientific validity determination and performance evaluation
- MEDDEV 2.7/1, Clinical evaluation — A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC
- BSI white paper, Explaining IVD classification issues
- BSI white paper, Risk management for medical devices and the new BS EN ISO 14971

About the author

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Dr Fiona Gould, PhD is a Medical Device Regulatory Affairs consultant focusing on the application of IVDR and MDR. She obtained her PhD in Cell and Molecular Biology from the University of Aberdeen (UK) in 2004 and has held positions in academia, the pharmaceutical and medical device industries predominantly in molecular biology research, project management and regulatory affairs. For the previous 3 years, Fiona has developed IVDR technical documentation for a broad range of device types and classifications for a large global IVD company. Fiona has also recently participated in a working group which successfully published recommendations for validation of pregnancy self-tests under IVDR.

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- *Person responsible for regulatory compliance (PRRC) – MDR/IVDR Article 15: An overview of the requirements and practical considerations,* Anne Jury and Maddalena Pinsi
- *Guidance on MDCG 2019-9: Summary of Safety and Clinical Performance,* Amie Smirthwaite
- *Clinical evaluation under EU MDR,* Amie Smirthwaite
- *Medical device clinical investigations – What's new under the MDR? An update,* Maria Donawa
- *Using Standards to Demonstrate conformity with Regulations,* Eamonn Hoxey

Forthcoming white papers

- *Requirements of EU-GDPR and PMCF studies, registries and surveys under the MDR* (working title), Richard Holborow
- *How to prepare for and implement the forthcoming IVDR – dos and don'ts,* Erik Vollebregt and Gert Bos, updated in 2022 by Steve Lee

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This paper was published by
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