**Disclaimer:**

This document was prepared by the Ad Hoc Commission “In Vitro Diagnostic Medical Devices” of the *Association of the Scientific Medical Societies in Germany* (AWMF) in accordance with Regulation (EU) 2017/746 Art. 5 (5). The document is not legally binding and serves solely as a recommendation for implementing the IVDR requirements in health institutions that manufacture and use devices. The document reflects the current state of knowledge at the time it was written and does not claim to be complete. The authors assume no liability whatsoever.

File name: AWMF\_IVDR\_Performance

Version: v.02

Date of issue: 28 September 2021

Authors: Dombrink, Isabel

Teubert, Anna

Eggermann, Thomas

The English translation was kindly supported by INSTAND (Dec 2021).

The implementation of a performance evaluation in medical laboratories (IH-IVD) as required by the IVDR

# Annex I Sections 5-8

The IVDR stipulates in Annex I, Chapter 1 - General Requirements (see Table 1) that devices should achieve the performance required for their intended use and that they should maintain this required level of safety throughout their lifetime.

Table 1 IVDR - Annex I, Chapter 1, Sections 1, 6-8 of the IVDR

|  |  |
| --- | --- |
| **IVDR** | |
| Annex I Chapter 1 | |
| *Section 1* | *Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.* |
| *Section 6* | *The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer’s instructions.* |
| *Section 7* | *Devices shall be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations in temperature and humidity, taking into account the instructions and information provided by the manufacturer.* |
| *Section 8* | *All known and foreseeable risks, and any undesirable effects shall be minimised and be acceptable when weighed against the evaluated potential benefits to the patients and/or the user arising from the intended performance of the device during normal conditions of use.* |

Risk management and performance evaluation intersect here since the achieved performance must also be compatible with the potential benefits of the device. Article 5 Section i) stipulates that an assessment of the experience gained from its clinical use should be made, which must also be taken into account in the course of the iterative risk management process.

Table 2 IVDR - Chapter 2, Article 5 of the IVDR

|  |  |
| --- | --- |
| **IVDR** | |
| Chapter 2 | |
| *Article 5 i)* | *The health institution shall review experience gained from the clinical use of the devices and take all necessary corrective actions* |

# Annex I Section 9

Section 9 of Annex I, Chapter 2 of the IVDR – Requirements Regarding Performance, Design and Manufacture - describes the respective performance characteristics.

Section 9.1 makes clear that the performance characteristics to be evaluated are linked to the intended purpose of the in-house IVD (IH-IVD). The evaluation of the performance characteristics must ensure that the device achieves the performance required for its intended purpose.

Section 9.2 requires that the performance characteristics be maintained throughout the lifetime of the device. This is ensured by internal controls which, for example, are assessed as part of the plausibility check of test results and can allow conclusions to be drawn about the performance of an examination procedure or IH-IVD. A further check of the performance characteristics can also be carried out through the medical validation of the test results. Likewise, external quality assurance measures, such as EQA schemes and interlaboratory comparisons serve as a way to monitor whether the performance characteristics are being maintained throughout the lifetime of the device.

Section 9.3 describes the requirements of the IVDR when the performance of the IH-IVD is linked to calibrators and/or control materials. For further guidance, see the Checklist for Annex 1 issued by the AWMF’s Ad Hoc IVD Group.

The requirements of Section 9.4 normally do not apply to in-house IVDs.

Table 3 IVDR - Annex I, Chapter II, Section 9 of the IVDR

|  |  |
| --- | --- |
| **IVDR** | |
| Annex I Chapter II | |
| *Section 9.1* | *Devices shall be designed and manufactured in such a way that they are suitable for the purposes referred to in point 2 of Article 2, as specified by the manufacturer, and suitable with regard to the performance they are intended to achieve, taking account of the generally acknowledged state of the art. They shall achieve the performance, as stated by the manufacturer and in particular, where applicable* |
| *a)* | ***the analytical performance****, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantification, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions and* |
| *b)* | ***the clinical performance****, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.* |
| *Section 9.2* | *The performance characteristics of the device shall be maintained during the lifetime of the device as indicated by the manufacturer.* |
| *Section 9.3* | *Where the performance of a device depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. Where available, metrological traceability of values assigned to calibrators and control materials shall be assured through certified reference materials or reference measurement procedures.* |
| *Section\* 9.4* | *The characteristics and performance of the device shall be specifically checked in the event that they may be affected when the device is used for the intended purpose under normal conditions:* |
| *a)\** | *for devices for self-testing, performance obtained by laypersons;* |
| *b)\** | *for devices for near-patient testing, performance obtained in relevant environments (for example, patient home, emergency units, ambulances).* |

\* These requirements normally do not apply to in-house IVDs.

Section 9.1 a) and b) are described in more detail below. Various parameters are listed for the analytical performance (9.1 a)) and clinical performance (9.1 b)) to be determined.

The points in Section 9.1 are to be met insofar as they apply to the device.

The parameters for analytical and clinical performance as per Annex I Section 9.1 are listed individually and described in more detail below. (*Please note: The definitions listed here are for guidance purposes only and are in no way intended to be exhaustive*):

Table 4 IVDR - Annex I, Chapter II, Section 9 a) and b) of the IVDR including definition and remarks by the authors

|  |  |  |
| --- | --- | --- |
|  | Definition | Remarks/interpretation by the authors |
| **Analytical performance** | Ability of a device to correctly detect or measure a particular analyte; |  |
| Analytical sensitivity | Analytical sensitivity is defined as the limit of detection, i.e., the smallest amount of the target marker that can be accurately detected. | In order to draw conclusions about the analytical sensitivity, it is necessary to consider, for example, the limit of quantification (LOQ) and limit of detection (LOD) as well as the measuring range and linearity. |
| Analytical specificity | Analytical specificity describes the extent to which the testing method measures only what it intends to measure. | If similar substances in the matrix influence the lab measurement, it is called a cross-reaction. |
| Trueness (bias) | The closeness of agreement between the measured value and the expected value. | The expected value can be determined using a reference material. For methods without a reference material, trueness can be verified in a comparison with another method and the agreement with this method can be reported. |
| Precision (repeatability and reproducibility) | Agreement between the different independent measurement results of a sample in a measurement series or between different measurement series (various factors such as user, device, reagent batch, etc. may vary). | Precision is indicated by the coefficient of variation (relative standard deviation). |
| Accuracy | Resulting from trueness and precision |  |
| Limits of detection | The limit of detection (LOD) is the smallest value that can be detected by this method. | LOD is sufficient for qualitative methods, whereas the LOQ should be determined for quantitative methods. |
| Limits of quantification | The lower limit of quantification (LLOQ) is the smallest determinable quantitative value that can be determined with an acceptable level of accuracy and precision. |  |
| Measuring range | Is defined by the LOQ and the linearity |  |
| Linearity | Represents the proportional relationship between concentration and measurement signal. | Important for quantitative methods, since this, together with the LOQ, indicates a method’s measuring range. |
| Cut off | The cut-off value divides the range of measured values into test positives and test negatives. | For example: a 95% positive cut-off value is the value at which 95% of the true positives are detected as positive. |
| **Clinical performance** | Ability of a device to provide results that correlate with a specific clinical condition or physiological or pathological process or state in a specific target population and in specific intended users; |  |
| Diagnostic sensitivity | The sensitivity of a diagnostic test is its ability to detect certain characteristics (e.g., disease). Sensitivity is defined by the quotient:  Sensitivity = (true positive) / (total number of patients) |  |
| Diagnostic specificity | The specificity of a diagnostic test is its ability to identify persons lacking certain characteristics (e.g., disease) as non-patients. Specificity is defined by the quotient:  Specificity = (true negative) / (total number of non-patients) |  |
| Positive predictive value | A device’s ability to separate true positives from false positives for a given attribute in a given population; | The predictive value is not only influenced by the sensitivity and specificity of a diagnostic test, but crucially also by the prevalence of the disease in the tested population. |
| Negative predictive value | A device’s ability to separate true negatives from false negatives for a given attribute in a given population; | The predictive value is not only influenced by the sensitivity and specificity of a diagnostic test, but crucially also by the prevalence of the disease in the tested population. |
| Likelihood ratio and expected values in non-affected and affected populations | The likelihood of a particular result occurring in a person with the clinical or physiological target condition relative to the likelihood of the same result occurring in a person without that clinical or physiological condition. |  |
|  |  |  |

In order to verify the analytical performance characteristics, commercially available or other well-characterised control samples can be used which reliably enable an objective assessment and calculation of the required parameters and are backed up by, for example, external quality assurance in the form of an EQAS. To verify the clinical performance characteristics, publications may be used, for example, provided that they can be applied to the IH-IVD under consideration with respect to test design, intended purpose and/or the process technology.

# Reference to Annex XIII

Even though IH-IVDs do not have to explicitly comply with Annex XIII of the IVDR, it can be used as a valuable source of information and guide for conducting the performance assessment as required by the IVDR.

The performance evaluation is described in Annex XIII of the IVDR as follows:

Table 5 IVDR - Annex XIII, Part A of the IVDR

|  |  |
| --- | --- |
| **IVDR** | |
| Annex XIII, *Part A* | |
| *Section 1* | *Performance evaluation of a device is a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer. To plan, continuously conduct and document a performance evaluation, the manufacturer shall establish and update a performance evaluation plan. The performance evaluation plan shall specify the characteristics and the performance of the device as well as the process and criteria applied to generate the necessary clinical evidence.*  *The performance evaluation shall be thorough and objective, considering both favourable and unfavourable data.*  *Its depth and extent shall be proportionate and appropriate to the characteristics of the device including the risks, risk class, performance and its intended purpose.* |

Further on, Annex XIII, Chapter 1, Section 1.2 describes how to demonstrate scientific validity and analytical and clinical performance (for CE-IVDs!).

The clinical evidence is to be based on the results of the assessment of scientific validity and analytical and clinical performance and is to be documented in a performance evaluation report as specified in Annex XIII. The scope of such a report is outlined in detail in Annex XIII, Chapter 1, Section 1.3.2.

As Annex XIII does not explicitly apply to IH-IVDs, the information in this Annex should be regarded as purely informative, however it can be used for guidance or assistance. For example, according to Annex I, which is compulsory, neither a performance evaluation plan nor a performance evaluation report is mandatory for IH-IVDs.

Part B of Annex XIII describes how to plan and document post-market performance surveillance. Even though the performance of IH-IVDs must be monitored throughout the lifetime of the device according to Annex I, Chapter 1, Section 6, the laboratory is not explicitly required to adhere to Part B of Annex XIII.

# Further requirements of Annex I that relate to performance

Even though the requirements relating to performance are mainly presented in Section 9 of Annex I “Requirements Regarding Performance, Design and Manufacture”, performance requirements are also outlined in other parts of Annex I (as shown for example in Table 6 and Table 7).

Table 6 IVDR - Annex I, Chapter 2, Sections 10.1, 13.1 and 14.1

|  |  |
| --- | --- |
| ***IVDR*** | |
| *Annex I Chapter 2* |  |
| *Section 10.1* | *Devices shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements referred to in Chapter I are fulfilled.* |
|  | *Particular attention shall be paid to the possibility of impairment of analytical performance due to physical and/or chemical incompatibility between the materials used and the specimens and/or the measurand or marker to be detected (such as biological tissue, cells, body fluids and micro-organisms), taking account of the intended purpose of the device.* |
| *Section 13.1* | *If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system, shall be safe and shall not impair the specified performance of the devices. Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instructions for use.* |
| *Section 14.1* | *Devices having a primary analytical measuring function shall be designed and manufactured in such a way as to provide appropriate analytical performance in accordance with Annex I, Section 9.1, point a, taking into account the intended purpose of the device.* |

Section 20.4 of Annex 1, Chapter 3 outlines the information required for the performance evaluation in the instructions for use (corresponding standard operating procedures are generally regarded here for IH-IVDs).

Table 7 IVDR - Annex I, Chapter 3, Section 20.4.1 of the IVDR

|  |  |
| --- | --- |
| **IVDR** | |
| Annex I Chapter 3 Section 20.4.1 | |
| *Section 20.4.1* | *The instructions for use shall contain the following information:* |
| *w* | *analytical performance characteristics, such as analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and measurement range, (information needed for the control of known relevant interferences, cross-reactions and limitations of the method), measuring range, linearity and information about the use of available reference measurement procedures and materials by the user;* |
| *x* | *clinical performance characteristics as defined in Section 9.1 of this Annex;* |
| *z* | *where relevant, clinical performance characteristics, such as threshold value, diagnostic sensitivity and diagnostic specificity, positive and negative predictive value;* |

Furthermore, the IVDR does not specify the form of performance evaluation documentation. Here, too, Annex XIII can serve as a good guide.