The European In Vitro Diagnostics Regulation

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novineon CRO GmbH has been supporting manufacturers in clinical and regulatory affairs since 2001

Preclinical research

- Usability
- Design verification and product validation

Clinical Studies

- Project management
- Monitoring
- Data management / Biostatistics

Clinical Evaluation

- Literature review
- Clinical evaluation plan
- Conducting the clinical evaluation
- Summary of Safety and Clinical Performance
- Quantitative clinical evaluation

Regulatory Affairs

- Biological evaluation
- Risk management and instructions for use
- International Regulatory Affairs
  - FDA submissions for medical devices
  - Health Canada submissions for medical devices

Post-Market Surveillance

- PMS plans and reports
- Post-market clinical follow-up
- OntoPMS

Performance Evaluation

Regulatory Affairs

- Planning and implementation of performance evaluation
- Systematic literature review
- Development of PMS and PMPF plans and reports
- Review/revision of risk analyses and instructions for use

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1 IVDR: Introduction and new risk classification

2 Performance evaluation: three pillars for clinical evidence

3 Clinical performance studies: purpose and requirements

4 Post-market surveillance: requirements and implementation

The views, thoughts, and opinions expressed in this presentation are based on our current understanding of the IVDR and are subject to change.

All information in this presentation have been prepared to the best of our knowledge and belief. The speaker points out that he assumes no liability for the accuracy, actuality and completeness. In particular, this presentation does not replace legal advice in individual cases.

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3 Clinical performance studies: purpose and requirements

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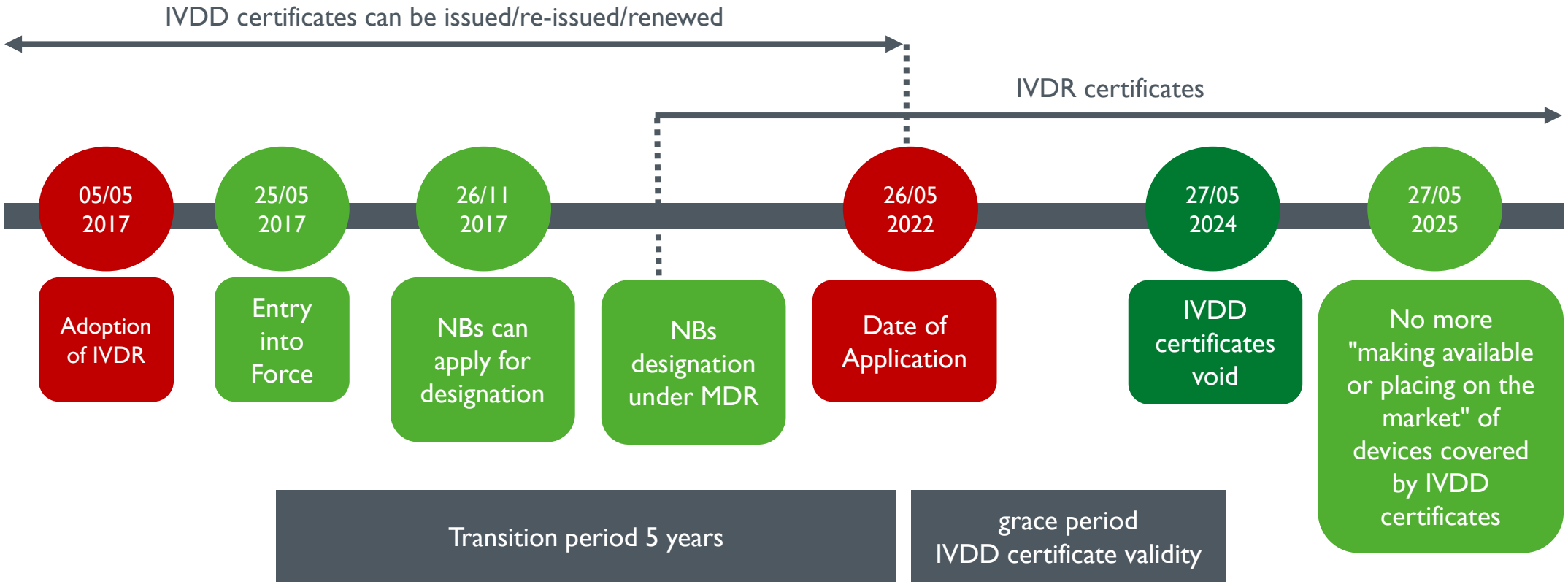
Only one year is left until date of application



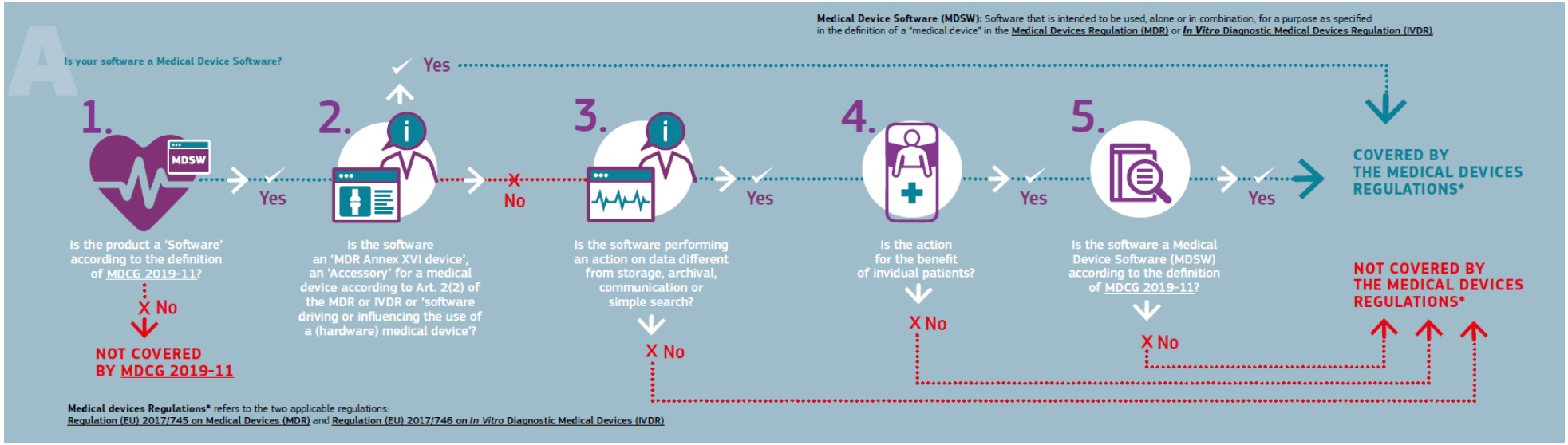
(EU) 2017/746, Art. 2

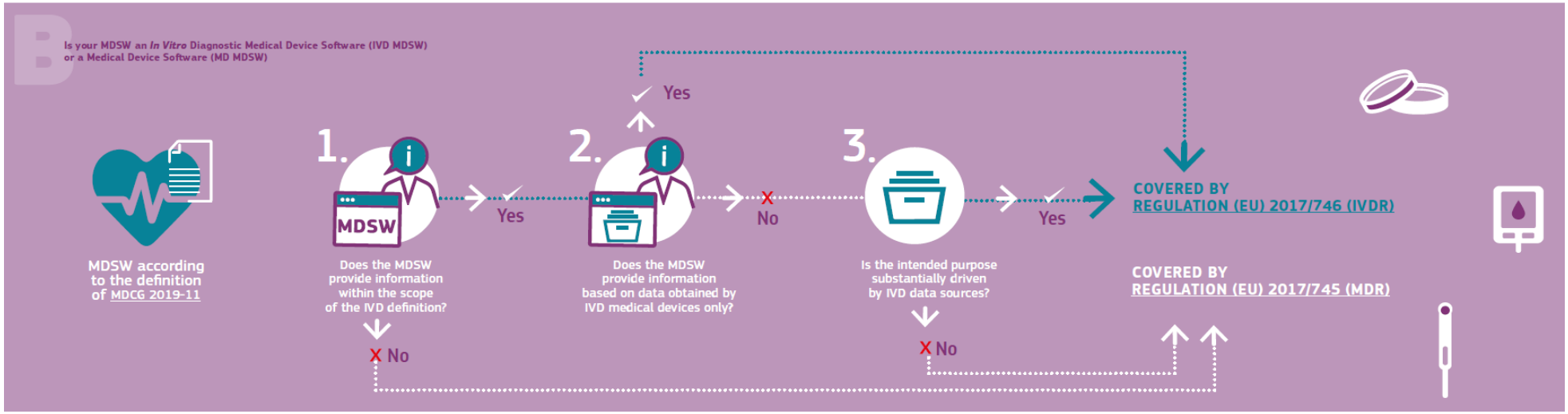
'*in vitro* diagnostic medical device' means any **medical device** which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, **intended by the manufacturer to be used *in vitro* for the examination of specimens**, including blood and tissue donations, derived from the human body, solely or principally **for the purpose of providing information** on one or more of the following:

a) concerning a physiological or pathological process or state;
b) concerning congenital physical or mental impairments;
c) concerning the predisposition to a medical condition or a disease;
d) to determine the safety and compatibility with potential recipients;
e) to predict treatment response or reactions;
f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices;

Is your software a Medical Device Software (MDSW)?





https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2021_mdsw_en.pdf

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The devices are categorized into four risk-based classes acc. to Annex VIII

IVDD
List-based approach

List A	List B	Unlisted
Detection of HIV infection	Blood sugar self-testing	Companion Diagnostics Detection of SARS-CoV-2

IVDR
Risk-based approach

Class D	Class C	Class B	Class A
Detection of HIV infection Detection of SARS-CoV-2	Companion Diagnostics Blood sugar self-testing	Detection of glucose in urine	Specimen receptacles

Near-patient testing (POCT) and MDSW are classified in their own right

MDCG 2020-16 Guidance on Classification Rules for in vitro Diagnostic Medical Devices under EU) 2017/745

Overview of the chapters and annexes in the IVDR

Chapter	
I	Introductory provisions
II	Making available on the market and putting into service of devices, obligations of economic operators, CE marking, free movement
III	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices
IV	Notified Bodies
V	Classification and conformity assessment
VI	**Clinical evidence, performance evaluation and performance studies**
VII	**Post-market surveillance, vigilance and market surveillance**
VIII	Cooperation between Member States, Medical Device Coordination Group, EU reference laboratories and device registers
IX	Confidentiality, data protection, funding and penalties
X	Final provisions

Annex	
I	General safety and performance requirements
II	Technical documentation
III	Technical documentation on post-market surveillance
IV	EU Declaration of conformity
V	CE marking of conformity
VI	Information to be submitted upon the registration
VII	Requirements to be met by notified bodies
VIII	Classification rules
IX	Conformity assessment based on a quality management system and on assessment of technical documentation
X	Conformity assessment based on type examination
XI	Conformity assessment based on production quality assurance
XII	Certificates issued by a notified body
XIII	**Performance evaluation, performance studies and post-market performance follow-up**
XIV	**Interventional clinical performance studies and certain other performance studies**
XV	Correlation table

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The data of the performance evaluation constitue the clinical evidence for the device

Clinical evidence

- To provide a body of clinical evidence to demonstrate conformity with the relevant general safety and performance requirements (GSPR)
- Clinical data and performance evaluation results to allow a qualified assessment whether the device achieves the intended **clinical benefit** and safety, when used as intended

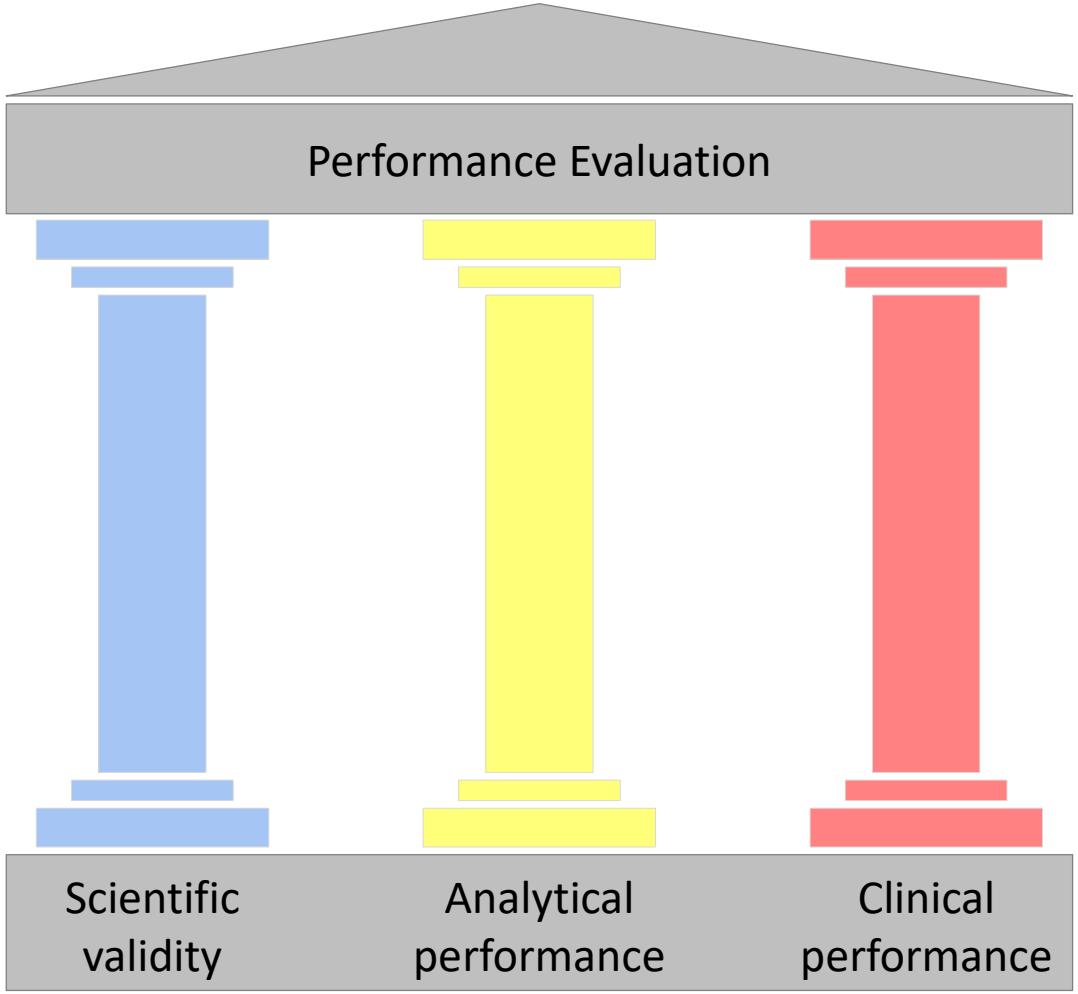
Performance evaluation means an assessment and analysis of data to establish or verify:

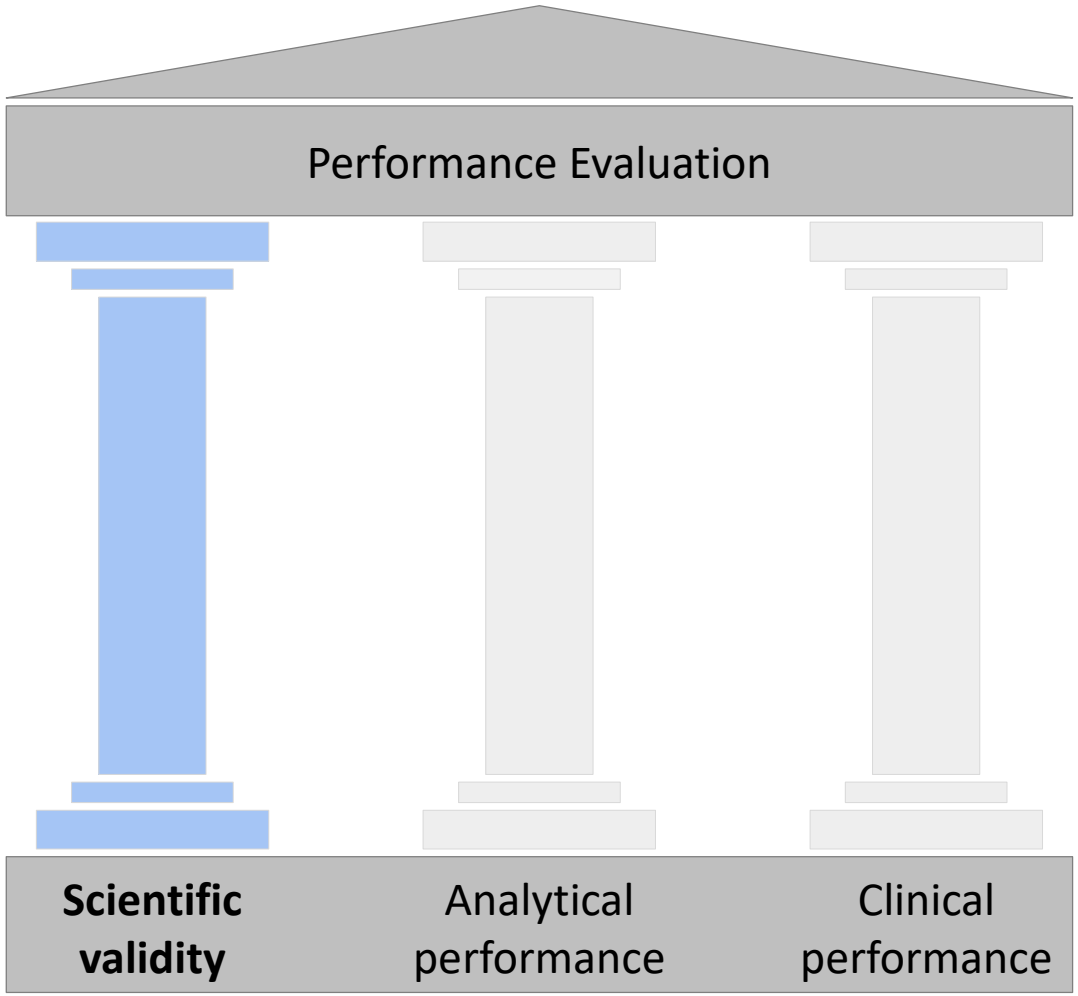
- the scientific validity
- the analytical performance and
- where applicable, the clinical performance of a device

Process of performance evaluation

- Required for each IVD, regardless of the product class, and part of the technical documentation
- Clearly defined in *Annex XIII, Part A*
- Done according to a performance evaluation plan
- Collated as a performance evaluation report
- Continuous during lifetime of the device

Data on scientific validity, analytical performance and clinical performance are assessed to provide clinical evidence for an IVD




Performance Evaluation
Scientific validity
Analytical performance
Clinical performance

Scientific validity

Scientific validity refers to the association of an analyte to a specific clinical condition or physiological state

- Relationship must be scientifically proven, even for established devices that have already been marketed under the IVDD
- Can be verified by means of a systematic and structured review of scientific literature
- Results are documented in the scientific validity report

Sources:

- Scientific (peer-reviewed) literature
- Information on similar devices measuring the same analyte or marker
- Technical standards
- Expert opinions/positions from relevant professional associations / medical society guidelines
- Results from proof of concept studies
- Results from clinical performance studies

Scientific validity must also be proven for established devices

Established and (non-)standardized tests

- Clinical guidelines or consensus for the use is available, international standard of reference material exist
- Examples: tests for liver markers (e.g. AST, ALT, bilirubin), metabolic markers (e.g. glucose, calcium), tests for infectious diseases (e.g. Hepatitis C), tumour markers (e.g. PSA)

Novel tests

- Tests are not established or standardized
- Involve a new analyte, new technology, new target population, new application of an established technology, or a new intended purpose
- Most likely, a clinical performance study will be required to demonstrate conformity with relevant GSPR
- Examples: tests for newly identified tumour markers (e.g. CTC), emerging infectious diseases (e.g. SARS-CoV-2)

Scientific validity can be verified by a systematic literature review

Systematic literature review:

- Description of the methodology used for the literature search
  → MEDDEV 2.7/1 revision 4
- Literature search protocol and report
- If applicable, justification why literature is excluded
- Appraisal of all relevant data
- Review and evaluation of the relevant data in the context of
  - medical background
  - state-of-the-art and
  - reference materials/measurements
- Information provided should be sufficient (quality) to enable an assessment of the scientific validity

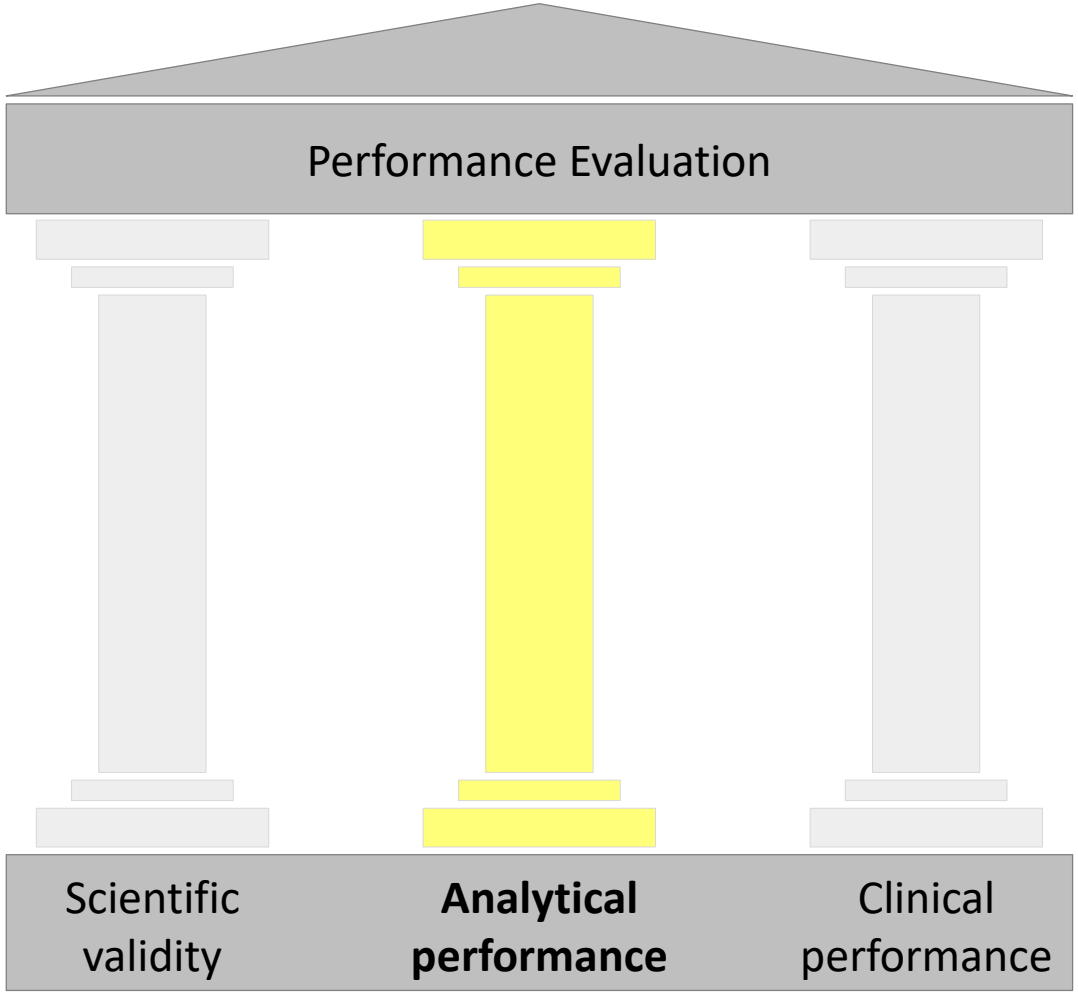
What is sufficient amount and sufficient quality of data?

Sufficient amount:

- Does the data support the intended use, indications, contraindications, target groups, intended user, clinical claims, residual risks and intended user environment?
- Have the clinical risks and analytical/clinical performance been investigated?
- Have relevant characteristics (e.g. cross-reactivity) been considered to support the performance of the device?

Sufficient quality:

- Are the type and design of study appropriate to meet the research objectives?
- Was the data set appropriate and actual (state-of-the-art)?
- Was the statistical approach appropriate to reach a valid conclusion?


Performance Evaluation
Scientific validity
Analytical performance
Clinical performance

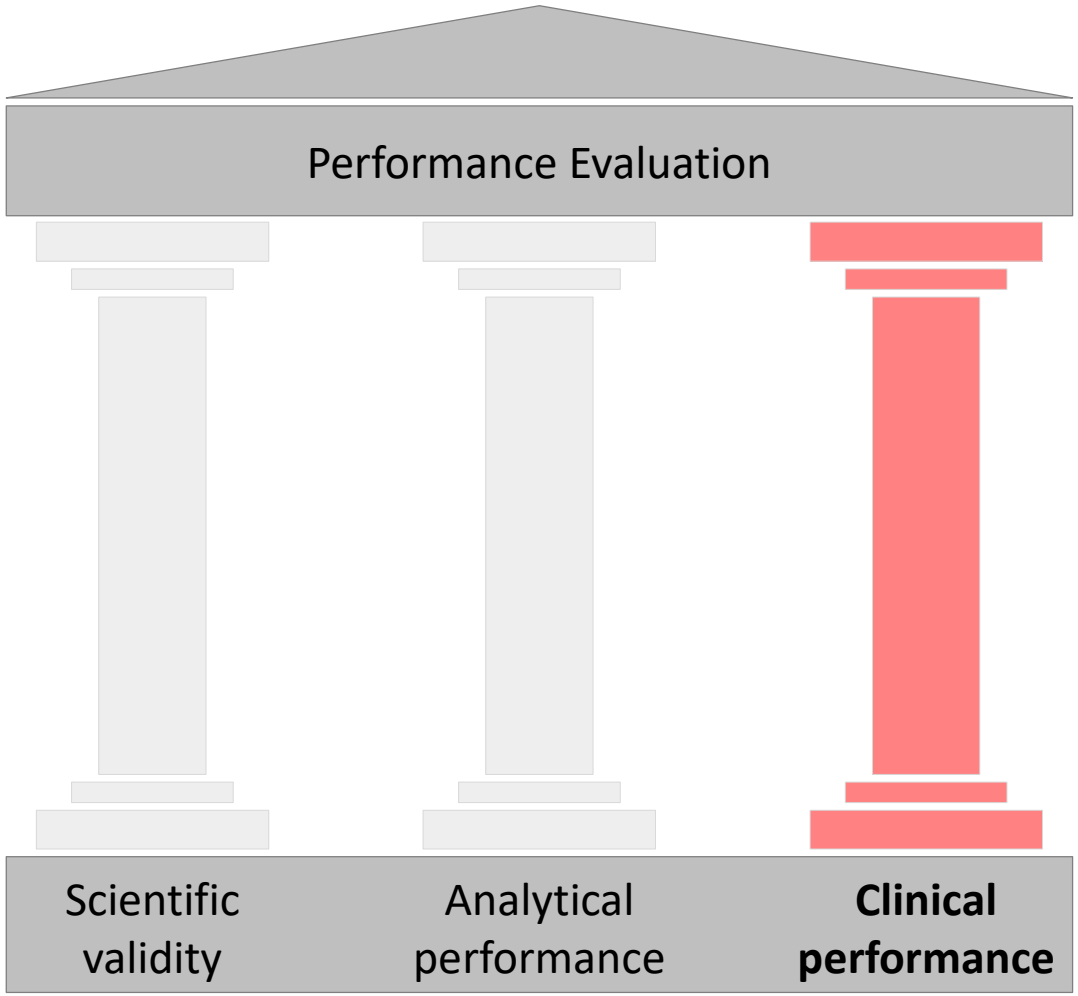
Analytical performance

Analytical performance is the ability of a device to correctly detect or measure a particular analyte

- Demonstration of analytical performance based on all parameters described in *point (a) of section 9.1 of Annex I*
- Generally verified by means of analytical performance studies
- For novel markers or markers without available reference material/measurement:
  - Comparison to other well-documented methods or the composite reference standard
  - Clinical performance study may be required comparing the performance of the novel device to the current standard in clinical practice
- Results are documented in the analytical performance report

Examples of characteristics to be verified

- Analytical sensitivity (e.g. limit of detection)
- Analytical specificity (e.g. interference, cross-reactivity)
- Cut-off values
- Absence of inacceptable cybersecurity vulnerabilities


Performance Evaluation
Scientific validity
Analytical performance
Clinical performance

Clinical performance

Clinical performance refers to the ability of a device to provide results that correlate with a specific clinical condition, a physiological or pathological process or state in a specific target population and specific intended users.

- Demonstration of analytical performance based on all parameters described in *point (b) of section 9.1 of Annex I*
- Clinical performance data can be derived from multiple sources:
  - Clinical performance studies
  - Scientific peer-reviewed literature
  - Published experience gained by routine diagnostic testing
- Clinical performance studies shall be performed unless it is duly justified to rely on other sources of clinical performance data
- Results are documented in the clinical performance report

Examples of characteristics to be verified

- Clinical / diagnostic sensitivity and specificity
- Usability

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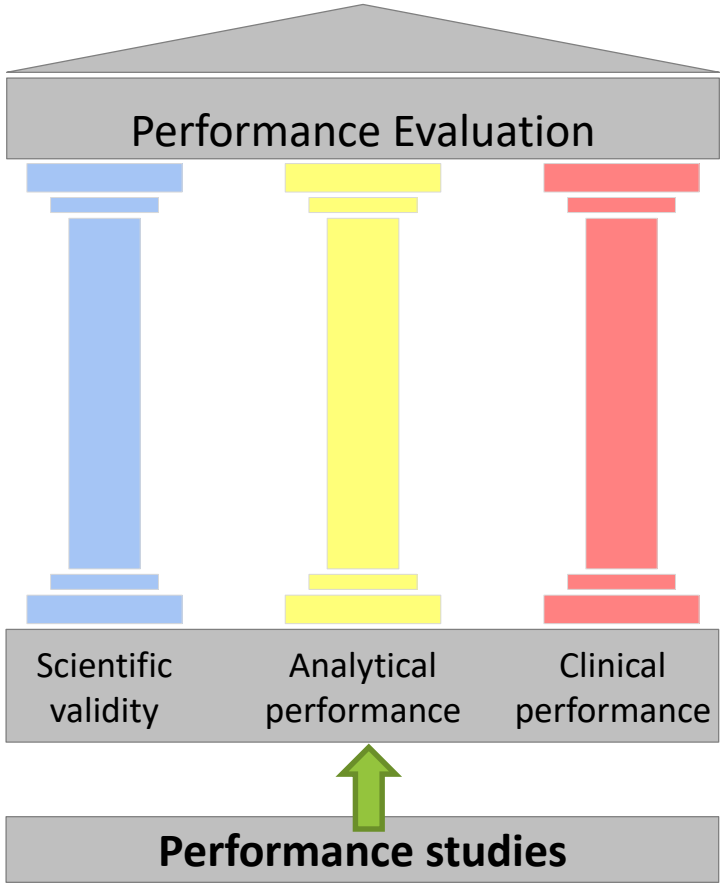
Clinical performance studies might be necessary to provide sufficient clinical evidence

The purpose of clinical performance studies is to establish or confirm aspects of device performance which cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing.



Regulatory requirements depend on the regulatory status of the IVD, the type of IVD and the used samples

General requirements

- IVDR
  - *Chapter VI, Art. 57*: General requirements regarding performance studies
  - *Annex XIII, Part A (2)*: Clinical performance studies
- ISO 20916: 2019 (In vitro diagnostic medical devices – Clinical performance studies using specimen from human subjects – Good study practice)
- Declaration of Helsinki (ethical principles for medical research involving human subjects)
- Additional requirements acc. to national law (e.g. MPEUAnpG in Germany)

→ For all IVDs

Additional requirements

- IVDR
  - *Chapter VI, Art. 58 – 77*

  Art. 58: Additional requirements for certain performance studies
  - *Annex XIV*: Interventional clinical performance studies and certain other performance studies

→
- Surgically invasive sample-taking
- Additional invasive procedures or other risks
- Interventional study
- Companion Diagnostics

General requirements apply to all clinical performance studies for all IVDs

Chapter VI, Art. 57

- Device complies with the GSPR apart from the aspects covered by the clinical performance study
- Performed in circumstances similar to the normal conditions of use
- Designed and conducted in a way that the rights, safety, dignity and well-being of the participants are protected
- Conducted in accordance with applicable law on data protection

Additional requirements include approval regulations

Chapter VI, Art. 58

- Approval by competent authority
- No negative opinion of ethics committee
- Sponsor or legal representative in EU
- Appropriate protection of vulnerable subjects and populations
- Anticipated benefits justify the foreseeable risks and inconveniences

Performance studies on vulnerable subjects and populations

- *Art. 60*: Performance studies on incapacitated subjects
- *Art. 61*: Performance studies on minors
- *Art. 62*: Performance studies on pregnant or breastfeeding women
- *Art. 63*: Additional national measures (e.g. persons performing military service)
- *Art. 64*: Performance studies in emergency situations

Annex XIII describes principles of clinical performance studies and their documentation

- Shall be carried out in accordance with recognized ethical principles → Declaration of Helsinki
- Maximize the relevance of the data while minimizing potential bias

Clinical performance study plan

- Detailed requirements in *Annex XIII, Part A, section 2.3.2.*
- For studies using left-over samples, some points are not applicable

Clinical performance study report

Annex XIII, Part A, section 2.3.3.

- Signed by medical practitioner or other authorized person
- Shall contain information on the study plan, results and conclusions
- Results and conclusions: transparent, free of bias, clinically relevant
- Understandable without reference to other documents
- Amendments or deviations, data exclusions with rationale

For clinical performance studies with left-over samples, no approval is required

Clinical performance studies with left-over samples

IVDR, Recitals (73)

- No approval by competent authority
- Companion diagnostics using only left-over samples: notification of competent authority (*IVDR, Art. 58, section 2.*)
- General requirements are applicable
- Additional requirements are applicable (data protection)
- Additional requirements according to national law: ethical review

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Data on the quality, performance and safety of an IVD throughout its entire lifetime

Post market surveillance (PMS) System

- Continuous surveillance measure to update the benefit-risk determination and to discover the need for corrective, preventive or field safety corrective actions
- Data source for the continuous process of performance evaluation

> Post market surveillance means the active and systematic gathering, recording and analyzing of relevant data on **quality, performance and safety** of an IVD

Process of post-market surveillance

- Required for each IVD, regardless of the product class. Part of the technical documentation
- Scope clearly defined in *Chapter VII, Section 1 and Annex III*
- Done according to a PMS-Plan
- For Class A and B: collated in a PMS-Report
- For Class C and D: collated as a Periodic Safety Update Report (PSUR) and Summary of Safety and Performance (SSP)
- Incorporates Post-Market Performance Follow-Up (PMPF) acc. *Annex XIII, Part B*
  - PMPF Plan
  - PMPF Evaluation Report
- Continuous during the lifetime of the device

Documentation related to the PMS-System

A B C D

PMS-Plan

Contents: See Annex III Section 1a and 1b (e.g., PMPF-Plan*)

PMPF Evaluation Report

PMS-Report (Art. 80)
- Updated when necessary
- Made available to notified body (NB) and competent authority (CA) upon request

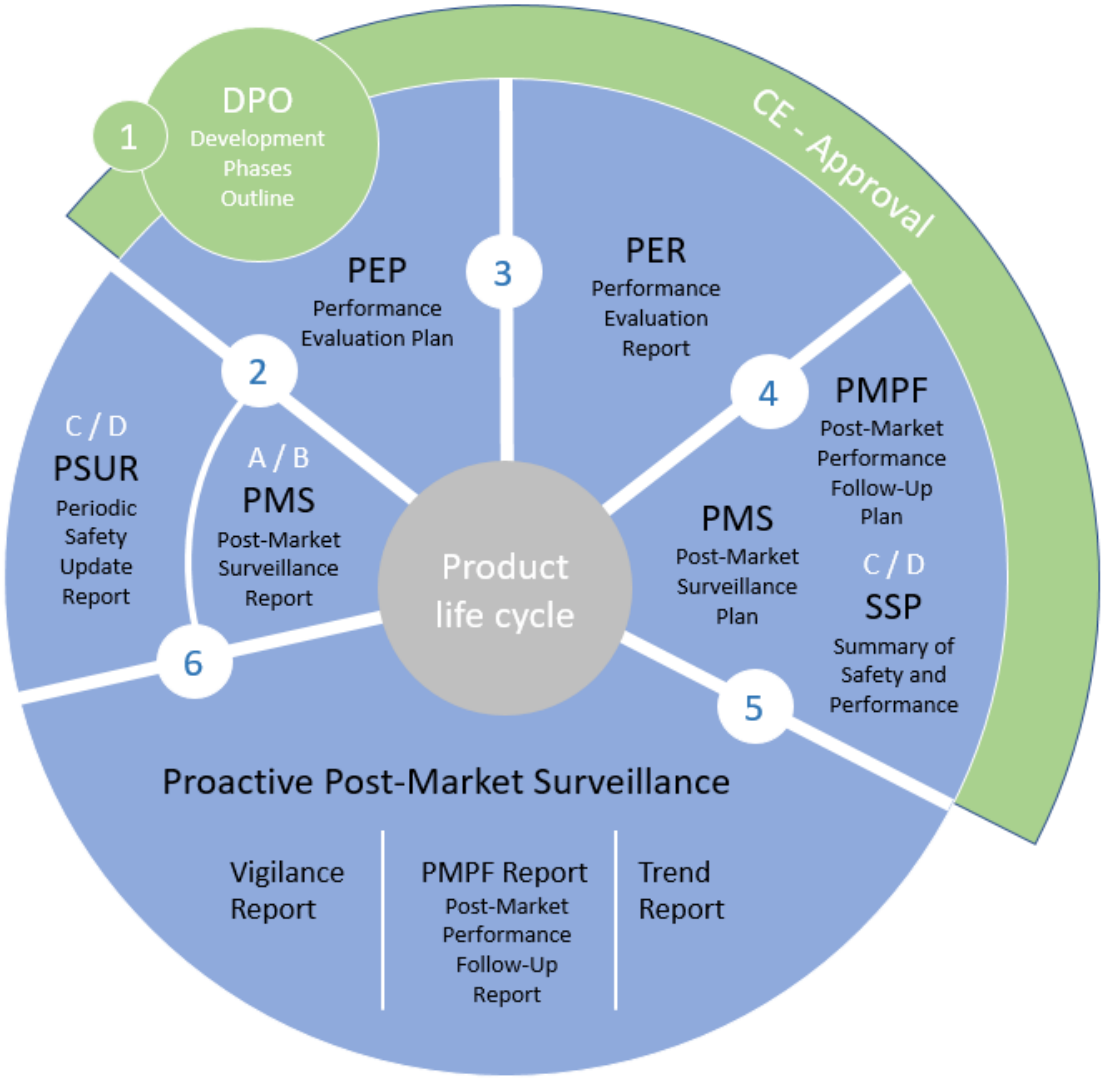
PSUR (Art. 81)
- Updated at least annually

- Class C
  Made available to NB and CA **upon request**
- Class D
  Submitted to the NB, made available to CA

SSP (Art. 29)
- Updated where necessary, as soon as possible
- Made publicly available

* Note: The contents of the PMPF-Plan are described in Annex XIII, Part B

Performance evaluation, post-market surveillance and risk management continuously update each other



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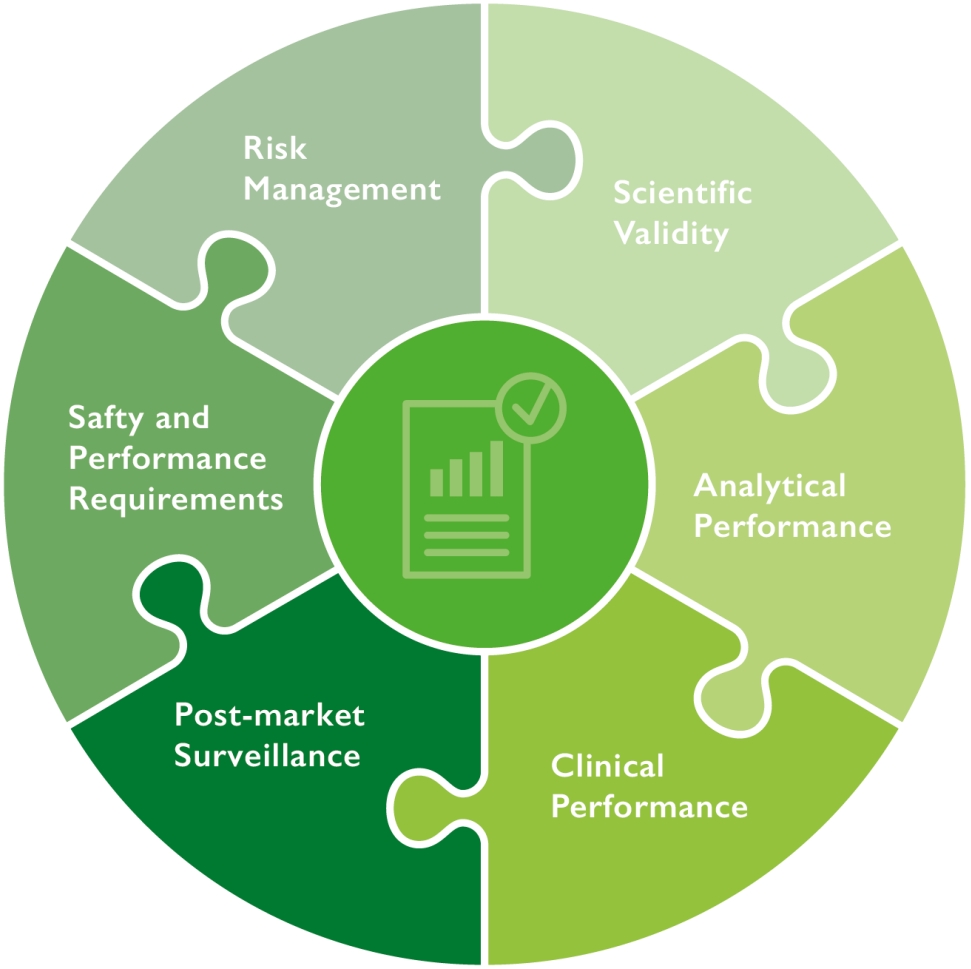
Got your pieces in place yet?



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