In-vitro Diagnostic Medical Devices Regulation in a nutshell (1/8)

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Directive 98/79/EC on in-vitro diagnostic medical devices → **Regulation on in-vitro diagnostic medical devices EU-IVDR 2017/746**

- The **Performance Evaluation** is a continuous process to demonstrate the scientific validity, analytical performance and clinical performance of an in vitro diagnostic medical device (IVD).
- The performance evaluation is conducted according to a Performance Evaluation Plan (PEP)
- The clinical evidence from the performance evaluation is documented in a **Performance Evaluation Report (PER)** as per **Art. 56** of the IVDR.

There are **NO** grandfathering provisions in IVDR. Therefore the transition from IVDD to IVDR shall be based on a thorough redesign of available documentation and creation of new according to the revised GSPRs

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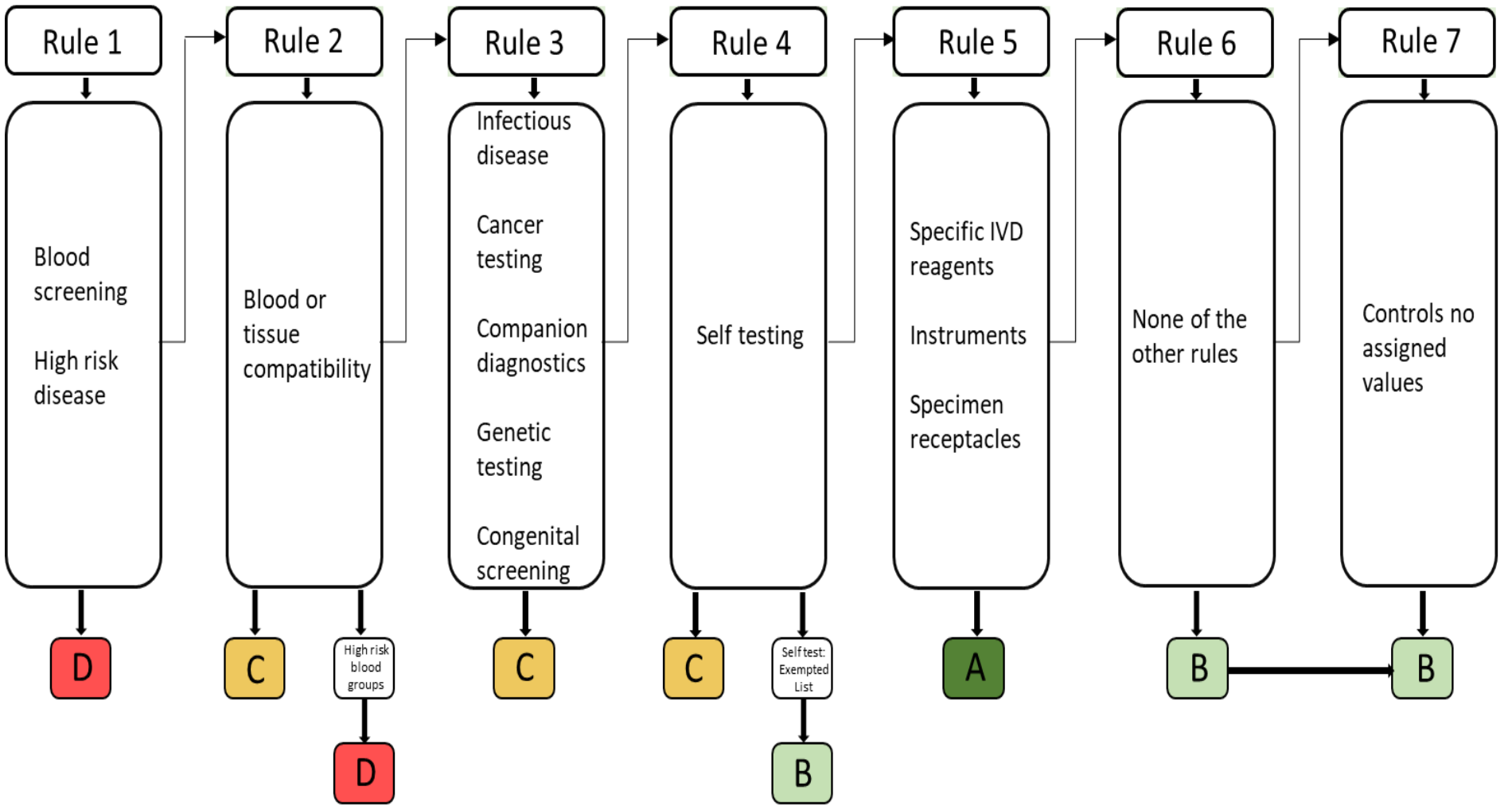
What is new? IVD Directive vs. IVD Regulation



In IVDR

- the only self-certified devices are the ones falling under Rule 5 (e.g. products for general laboratory use, buffers, general culture media, histological stains, instruments for IVD procedures and specimen receptacles)
- products falling under rule 6 (i.e. the ones not covered by any other Rule) require Notified Body certification

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Changes in Classification of IVDs

- Manufacturer proposes the classification based on the intended purpose. A notified body shall verify this proposal for classes A sterile, B, C, and D
- In case of a dispute, national Competent Authorities arbitrate

High Risk

Class D

- **High individual risk AND high public health risk**
- **IVDS:** ABI blood grouping, HIV blood diagnostic test, hepatitis B blood donor screening

Class C

- **High individual risk AND/OR medium public health risk**
- **IVDs:** HLA typing, PSA screening, blood glucose self-testing

Class B

- **Moderate individual risk AND/OR medium public health risk**
- **IVDs:** inflammatory markers, pregnancy tests, clinical chemistry, cholesterol self-testing ****self-test, which are not class C**

Class A

- **Low individual risk AND low public health risk**
- **IVDS:** specimen receptables, prepared selective culture; ****unless sterile, class A does not require NB involvement**

Low Risk

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What is new? IVD Directive vs. IVD Regulation

A

Definition & scope

- ❑ Applies to all IVDs & accessories
- ❑ New definitions & rules for companion diagnostics, in-house tests, kits, single-use IVDs, distance sales

B

Stakeholders

- ❑ Apart from Manufacturers, Notified Bodies & Competent Authorities, there are explicit roles for distributors and importers

C

Essential Requirements

- ❑ More detailed description of ERs
- ❑ Harmonized Standards & Common Specifications expected to play key role
- ❑ Specific rules: self-testing & NPT IVDs, CDx, genetic tets, in-house tests

D

Evidence

- ❑ Clarification of performance indicators (scientific validity, analytical & clinical performance)
- ❑ Explicit requirement to collect analyse clinical evidence throughout the life-cycle of a IVD

E

Clinical Studies

- ❑ Clinical performance studies required although some exceptions apply
- ❑ Focus on transparency of data from clinical performance studies

F

CE marking/conformity assessment

- ❑ NB involvement in all classes except class A, non-sterile
- ❑ Involvement of EMA & reference laboratories

G

Post-market requirements

- ❑ Post-market follow-up plan (PMPF) requirements
- ❑ Continuous updates of the PER

H

Transparency & traceability

- ❑ EUDAMED will be accessible to public and stakeholders
- ❑ Unique Device Identifier (UDI) for traceability in the supply chain

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Performance Evaluation Plan (PEP)

The PEP shall specify the characteristics and the performance of the device and the process and criteria applied to generate the necessary clinical evidence.
Annex XIII, part A, §1.1

A PEP shall include:

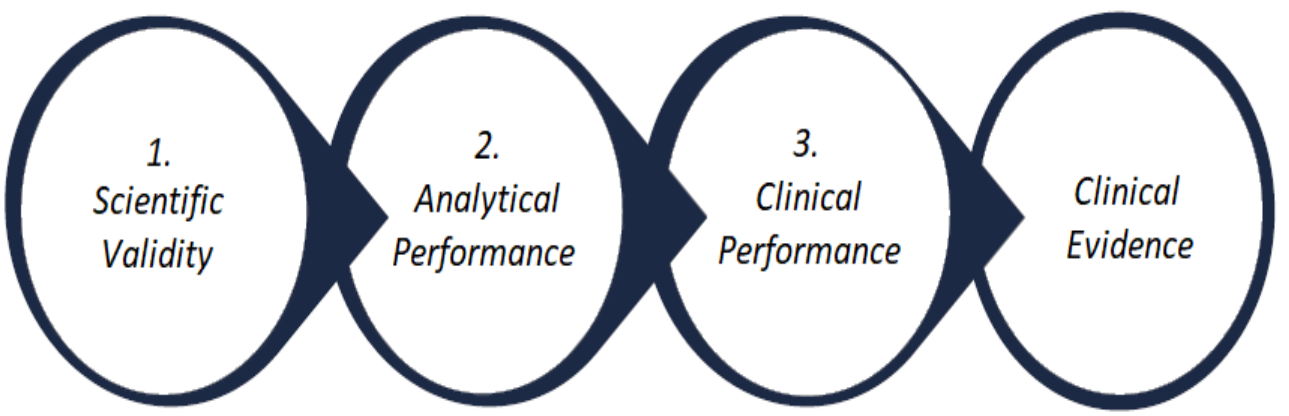
- ❑ Intended Purpose/Use
- ❑ Device description/characteristics
- ❑ Analyte/marker to be determined
- ❑ Certified reference materials/measurement procedures
- ❑ Labelling statements(indication, contrainidctaions, intended user etc.)
- ❑ Identification fo the applicable General Safety and Performance Requirements (GSPRs)
- ❑ Performance Evaluation Methodology
- ❑ Framing of the State of the Art
- ❑ Risk Management (Benefit-risk profile)
- ❑ Reference Databases (if software)
- ❑ Outline of developmental phases
- ❑ Post-Market Surveillance (PMS) & Post-Market Performance Follow-Up (PMPF) plans

Performance Evaluation Report (PER)

According to Annex XIII, part A, §1.3.2, the performance evaluation report shall include:

- ❑ the justification for the approach taken to gather the clinical evidence;
- ❑ the literature search methodology and the literature search protocol and literature search report of a literature review;
- ❑ the technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety;
- ❑ the nature and extent of the scientific validity and the analytical and clinical performance data that has been evaluated;
- ❑ the clinical evidence as the acceptable performances against the state of the art in medicine;
- ❑ any new conclusions derived from PMPF reports in accordance with Part B of Annex XIII

A PMPF plan is mandatory for all IVDs and yearly updates are required for classes C and D



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The 3 pillars of the Performance Evaluation Report (PER)

Scientific Validity

The association of an analyte to a clinical condition or a physiological state.

Research Question: What is the evidence for the association between the analyte/biomarker and the clinical condition?

Answer will be based on: Literature review, Expert opinion, Internal studies (e.g. proof of concept studies), nnformation from similar devices.

Analytical Performance

The ability of a device to correctly detect or measure a particular analyte.

Research Question: How good is the device at detecting the analyte/biomarker?

Answer will be based on: Literature review, internal study reports (e.g. analytical specificity, sensitivity, trueness/bias, precision, accuracy, limits of detection & quantitation, measuring range, linearity, thresholds/cut-off, interfering substances, cross-reactions, criteria for specimen collection and) handling.

Clinical Performance

The ability of a device to yield results that are associated with a particular clinical condition or a physiological process or state in accordance with the target population and intended user.

Research Question: How good is the device at determining who is positive with the clinical condition?

Answer will be based on: Literature review, Internal studies (on e.g. diagnostic sensitivity, diagnostic specificity, predictive values, likelihood ratio, expected population values), routine diagnostic testing, equivalent devices (if applicable)

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EU Reference Laboratories

Eligibility Cirteria

- **Horizontal roles:** provision of scientifc guidance, contribution to development of analytical methods
- **Regulatory responsibilities:** verification of performance, compliance with Common Specifications and batch testing for class D devices
- To be designated by the Commission
- Subject to on-site audits by the Commission

''In-house'' exemption

- Exemption of devices manufactured and used in the same Health Institution from the Regulation but subject to the GSPRs
- No transfer to other legal entities
- Requires accreditation of the laboratory
- The Health Institution to maintain documentation of the manufacturing process of the device and provide a rationale why the patients' needs cannot be met with an already marketed device

Conformity Assessment

- Class A: self-certified unless sterile
- Class B, C and D: Assessment of QMS and Technical Documentation by a Notified Body
- Additionally for class D:
- An EU designated Laboratory has to verify claimed performance and compliance with applicable Common Specifications
- If Common Specifications are not available or if the device is to receive its first certification, a consultation of expert panel is required (scrutiny mechanism)
- Companion diagnostics: A consultation procedure with a pharmaceutical authority is required

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Literature Review and State of the Art

As a general principle, the manufacturer shall identify through a systematic scientific literature review the available data relevant to the device and its intended purpose.

Annex XIII, part A, §1.2