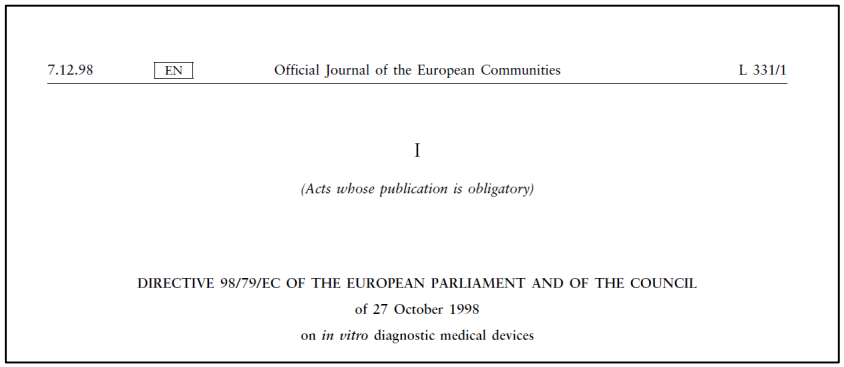
What you should know about the new
In Vitro Diagnostic Medical Device Regulation
Regulation (EU) 2017/746

Alex Lefevre, June 15th 2019

From EC Directive to EU Regulation

First EU law on in vitro diagnostics

- EC Directive 98/79/EC on IVDs is over 20 years old.



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I

(Acts whose publication is obligatory)

DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 27 October 1998
on *in vitro* diagnostic medical devices

- Lack of harmonisation: EU countries interpret rules differently
- Implementation in Belgium (KB 14/11/2001, BS 12/12/2001)
- Not adapted to recent technical and scientific progress.

EU IVD Directive

The rules we have today

Definition and scope

- Applies to all IVDs and their accessories
- Definition: relates to medical device def.
- No definition of Companion Diagnostic

Key stakeholders

- Manufacturers, Notified Bodies and Competent Authorities play key roles
- No advisory bodies

Classification

- List-based (Annex II, A or B)

Essential requirements

- High level description of essential requirements (same as in Medical Directive)
- Harmonised standards play a big role
- Specific rules for self-testing IVDs

Evidence

- Limited requirements
- 'Adequate performance data showing performance claimed by manufacturer'

Clinical studies

- Clinical studies not required

CE-marking / conf. assessment

- Annex II IVDs: Notified Body involved
- Other IVDs: subject to self-certification by manufacturer without Notified Body involvement

Post-market obligations

- Post-Market Surveillance (PMS) and vigilance system required

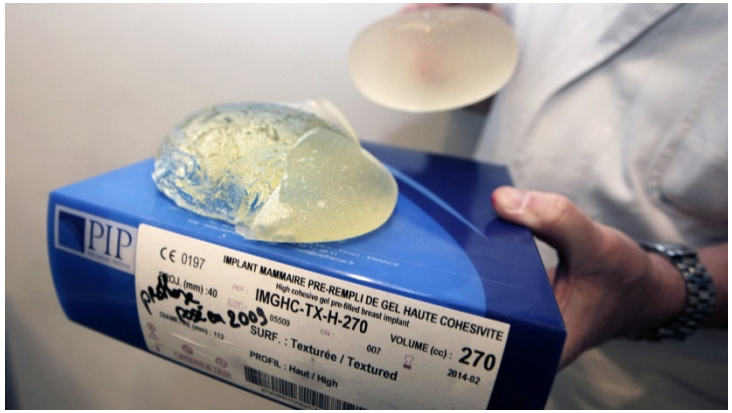
Transparency & traceability

- Eudamed accessible only to authorities
- Transparency of data not regulated
- Traceability not regulated

The road towards a new EU IVD Regulation

EU public consultation started already in 2008, BUT …

2010: PIP breast implant scandal.



2011: WHO recalls SDB HIV kits

Kenya recalls 'faulty' South Korean HIV kits

29 December 2011

Kenya has recalled one million HIV testing kits because of fears about their accuracy, a health official has said.

The WHO had raised an alert about the kit after finding half the test results could be wrong, said Shahnaz Sharif.

The South Korean company, however, says it volunteered to withdraw the kits and that the problem is that they give "invalid" results, rather than ones which are inaccurate.

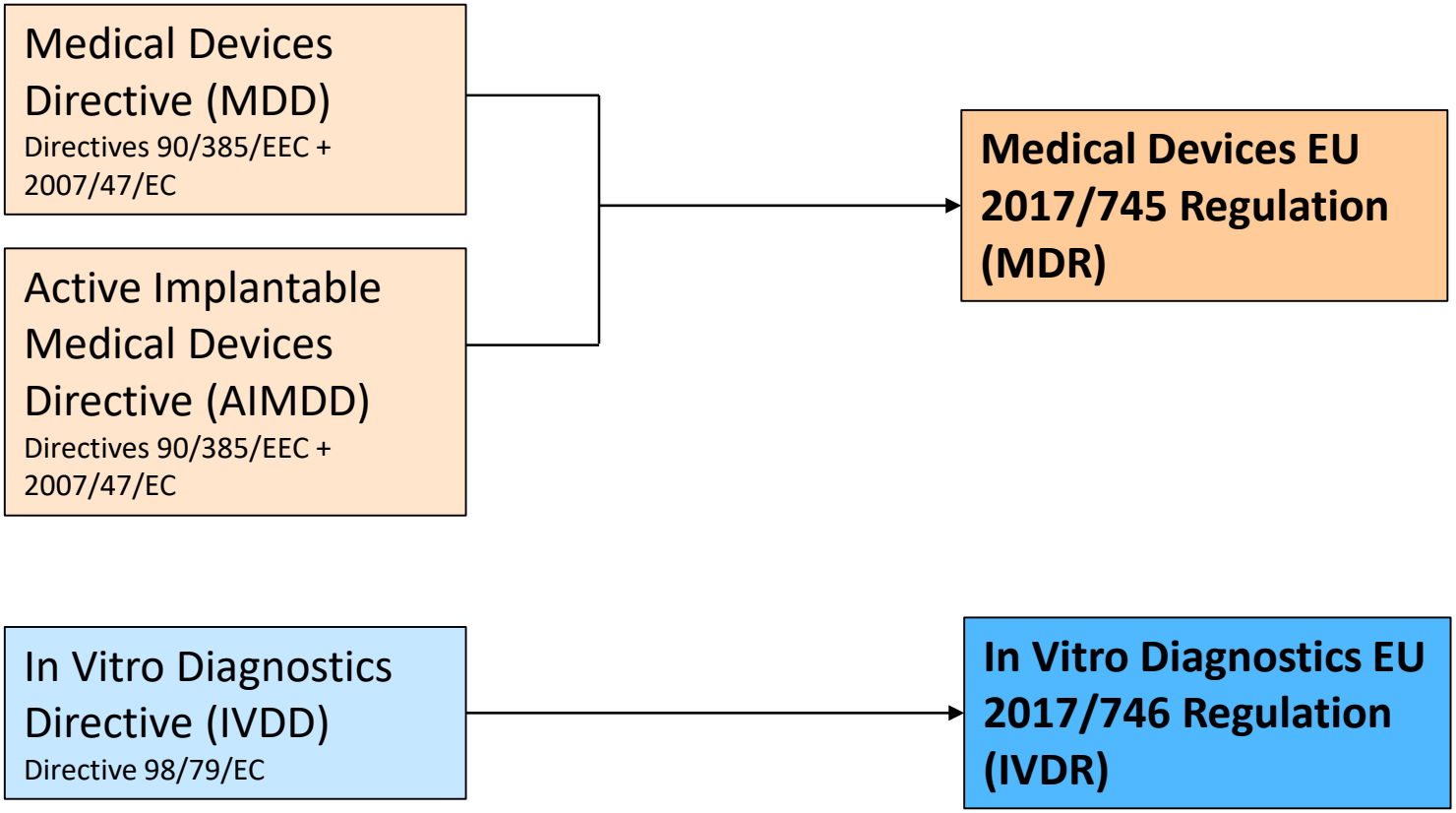
There has been a sharp increase in the number of Kenyans who go for HIV tests

Notified Body system heavily criticized

On the table: market authorization for medical devices and IVDs in the EU

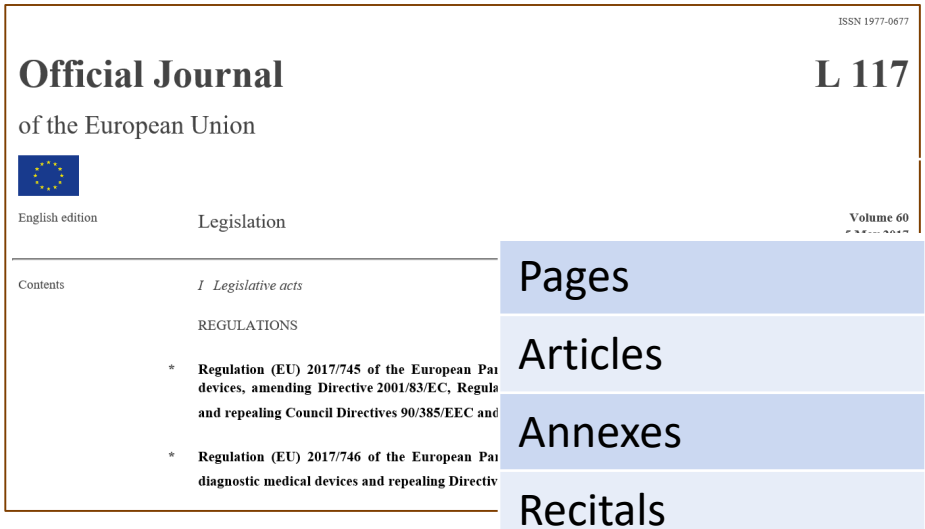
EU MDR & IVD Regulation

A new legal framework to enhance patient safety, with greater transparency and more information for the patient



(EU) 2017/746 Regulation

Published on May 5th 2017



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* **Regulation (EU) 2017/746 of the European Par diagnostic medical devices and repealing Directiv**

	IVDD (98/79/EC)	IVDR (2017/746)
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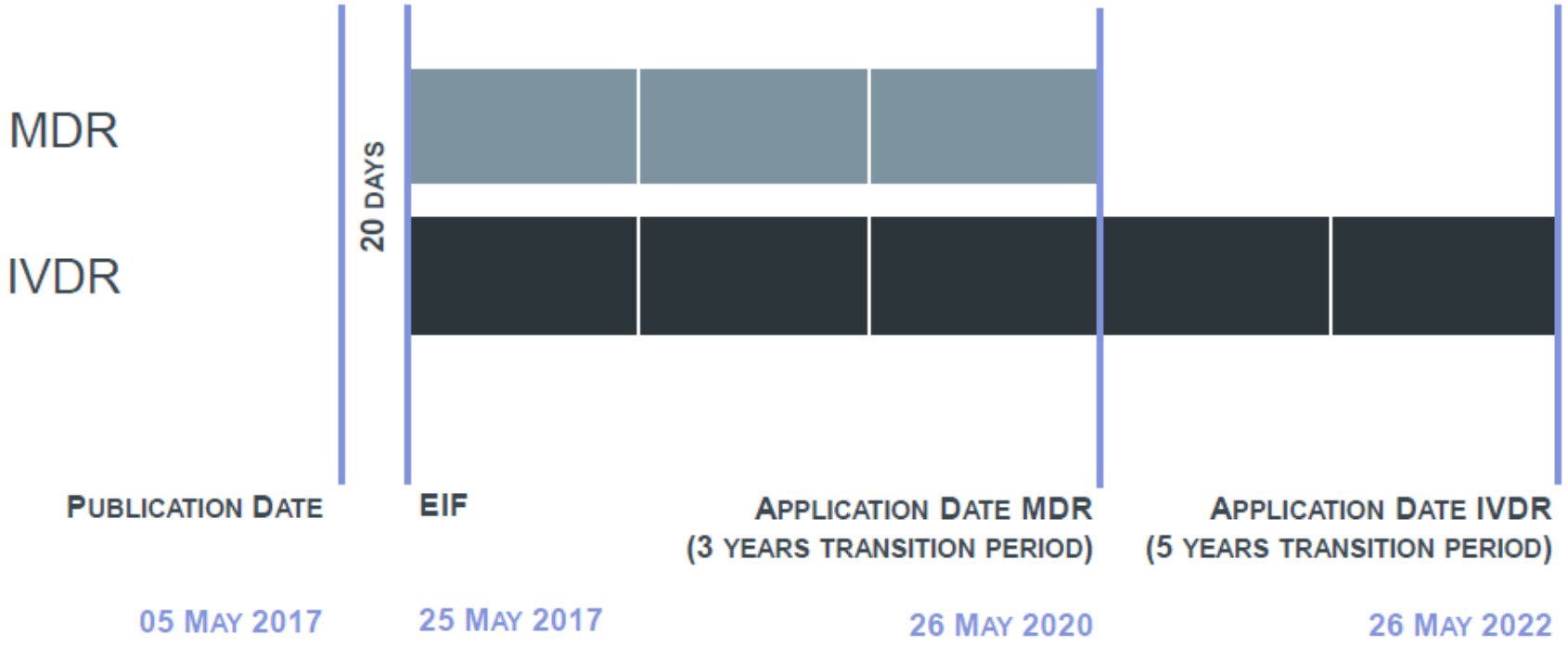
PMS & vigilance	400 words	5000 words

Based on Internal document QARAD

http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2017.117.01.0176.01.ENG

IVDR transition period

IVDR – From 25 May 2017 to 26 May 2022 (5 years)



At the moment, there are more than 40.000 different IVD products on the European market

EU IVD Regulation
What will it bring to stakeholders?

- **For the public/patients**
  - Safer devices and more transparency
- **For manufacturers/distributors**
  - Obligation to generate sufficient evidence that product is safe and performing as intended
  - Following up the safety and performance of the product when on the market (internal processes)
  - More public/media scrutiny of public product information
- **For notified bodies**
  - Stricter requirements concerning expertise and processes, more oversight
  - Some will go out of business → 'Traffic jam' at Notified Bodies?

The IVDR does not apply to

- Products for general laboratory use of **research-use only products**

  unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for IVD examination (→ Class A)

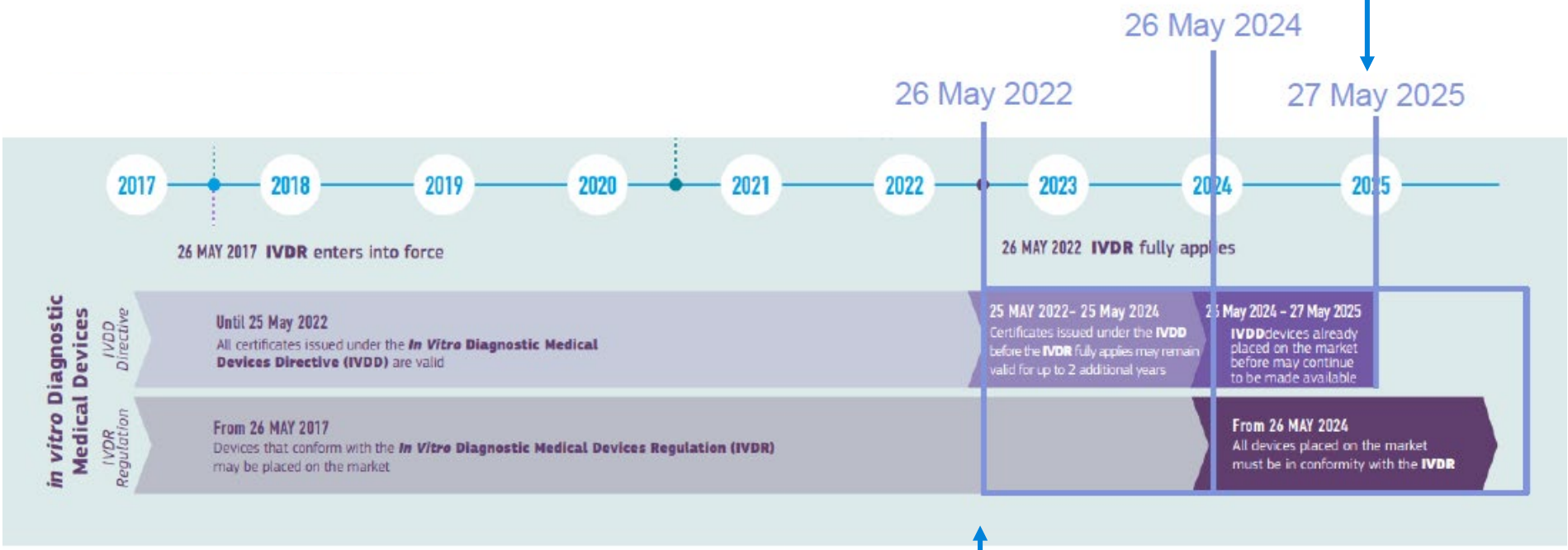
- **Invasive sampling products** or products which are directly applied to the human body for the purpose of obtaining a specimen.

- **Internationally certified reference materials**

- **Materials used for external quality assessment schemes**

IVDR transition period

Last date of putting into service or making available on the market IVDD compliant products placed on the market before Date of Application



Hard stop for all self declared IVDs

Competent bodies and authorities under the IVDR

Focus on the situation in Belgium

Since **November 2018**

- The FAMHP is officially in charge of proposing legislation relating to, and ensuring the follow-up, the application and the control of, the MDR and IVDR.
  And to clarify the grey zone within the EU IVDR (field vs legislation)
- Division of the Directorate-General POST & INSPECTION (FAMHP) have an IVD working group (with professionals of the laboratories (WG IVDR Sciensano) and the industry (beMedTech).
- *FAHMP already visited 20 (hospital) labs to get feedback on the IVDR.*
- Sciensano retains wide powers regarding the following: give opinions to the health authorities, support clinical research, scientific expertise, laboratory certification and rules of good laboratory practice, risk assessment.

Old vs New definition of a 'IVD medical device'

EU IVD medical devices directive 98/79 (IVDD)

- Current definition of "in vitro diagnostic medical device"

  - Reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system

  - **Intended purpose**: 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:

    Concerning a physiological or pathological state, or
    Concerning a congenital abnormality, or
    To determine the safety and compatibility with potential recipients, or
    To monitor therapeutic measures.

- Implemented as such in Belgium

EU IVD medical devices regulation 2017/746 (IVDR)

- New definition of "in vitro diagnostic medical device"

  - Reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system

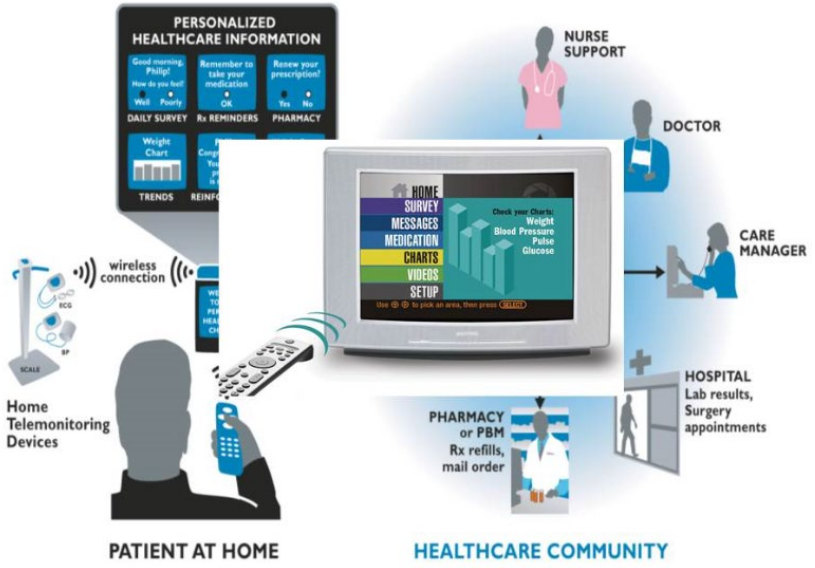
  - **Intended purpose**: to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body

  - Solely or principally for the purpose of providing information on one or more of the following:

    Concerning a physiological or pathological process or state, or
    Concerning congenital, physical or mental impairments, or
    Concerning the predisposition to a medical condition or a disease,
    To determine the safety and compatibility with potential recipients, or
    To predict treatment response or reactions, or
    To define or monitor therapeutic measure

An example of a medical device

The same is applicable for an IVD



Stand alone blood pressure wearable

Is NOT considered as an medical device

Blood pressure wearable sending information to a HCP and used to give advise to the patient

Is considered as an medical device

Change of 'IVD medical device' definition

Examples of (new) products falling under the IVDR

'Predicting treatment response or reactions'

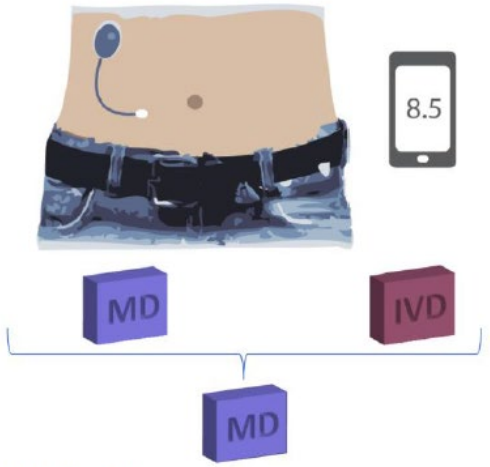
- Some lifestyle tests / nutrigenetic tests – with indirect medical purpose – which are currently not covered by the IVDD

'Predisposition to a medical condition or a disease'

- Tests measuring predisposition for medical treatment susceptibility
- Genetic tests
- Tests that provide information to predict treatment response or reactions such as companion diagnostics

'Software' (now explicitly mentioned in the definition)

- e.g. Hypodermal blood glucose sensor (MD)
- +App with glucose calculator (IVD) to analyse how much glucose the blood contains → meets the definition of an IVD
- If put on the market as a single product = MD (2017/745), **but** with an IVD component (the software – 2017/746) then MD



Key points

Horizontal aspect:
alignment IVD and MD Regulation

- Notified bodies
- Economic operators
- Post-Market surveillance
- Vigilance
- Market surveillance
- Traceability, UDI and registration
- Summary of safety and performance
- Transparency

Specific modifications:
specificities of the IVD

- Classification rules
- Conformity assessment
  - reference laboratory / experts / medicines agency
  - technical documentation examination
- Devices for self-testing
- Devices for near-patient testing
- Companion diagnostics
- Genetic tests
- Health apps with IVDs

EU IVD Directive vs. IVD Regulation

What's new?

Definition and scope

- Applies to all IVDs and their accessories
- Definition: relates to medical device def.
- New definitions and rules for: companion diagnostics (CDx), in-house tests, kits, single use IVDs, distance sales

Key stakeholders

- Manufacturers, Notified Bodies and Competent Authorities play key roles
- Several new bodies involved (MDCG, reference laboratories, EMA)
- Explicit roles for distributors, importers

Classification

- No longer list-based (Annex II, A or B)
- Risk-based (A-D)

Essential requirements

- A more detailed description of essential requirements than in current Directive
- Harmonised standards and Common Specifications play a big role
- Specific rules: self-testing & NPT IVDs, CDx, genetic tests, in-house tests etc.

Evidence

- Clarification of performance indicators (scientific validity, analytical & clin.perf.)
- Explicit requirement for clinical evidence, to be collected and analyzed throughout the life-cycle of an IVD
- Performance Evaluation Report (PER)

Clinical studies

- Clinical performance studies required (with some exceptions)
- Some studies require prior authorisation by authorities

CE-marking / conf. assessment

- Notified Body involved for all IVDs except risk class A (unless sterile)
- Involvement of EMA and reference laboratories (for some products)

Post-market obligations

- A pro-active and planned approach by the manufacturer to prove an IVD's safety and performance
- Post-Market Follow-up Plan (PMPF)
- Continuous updates of the PER

Transparency & traceability

- Eudamed database accessible to several stakeholders including to the public
- Transparency of data from clinical performance studies & class C and D
- Unique Device Identifier (UDI) to ensure traceability in the supply chain

Classification under the IVDR – 4 risk classes

IVD Directive: 'list based' (in order of increasing risk)

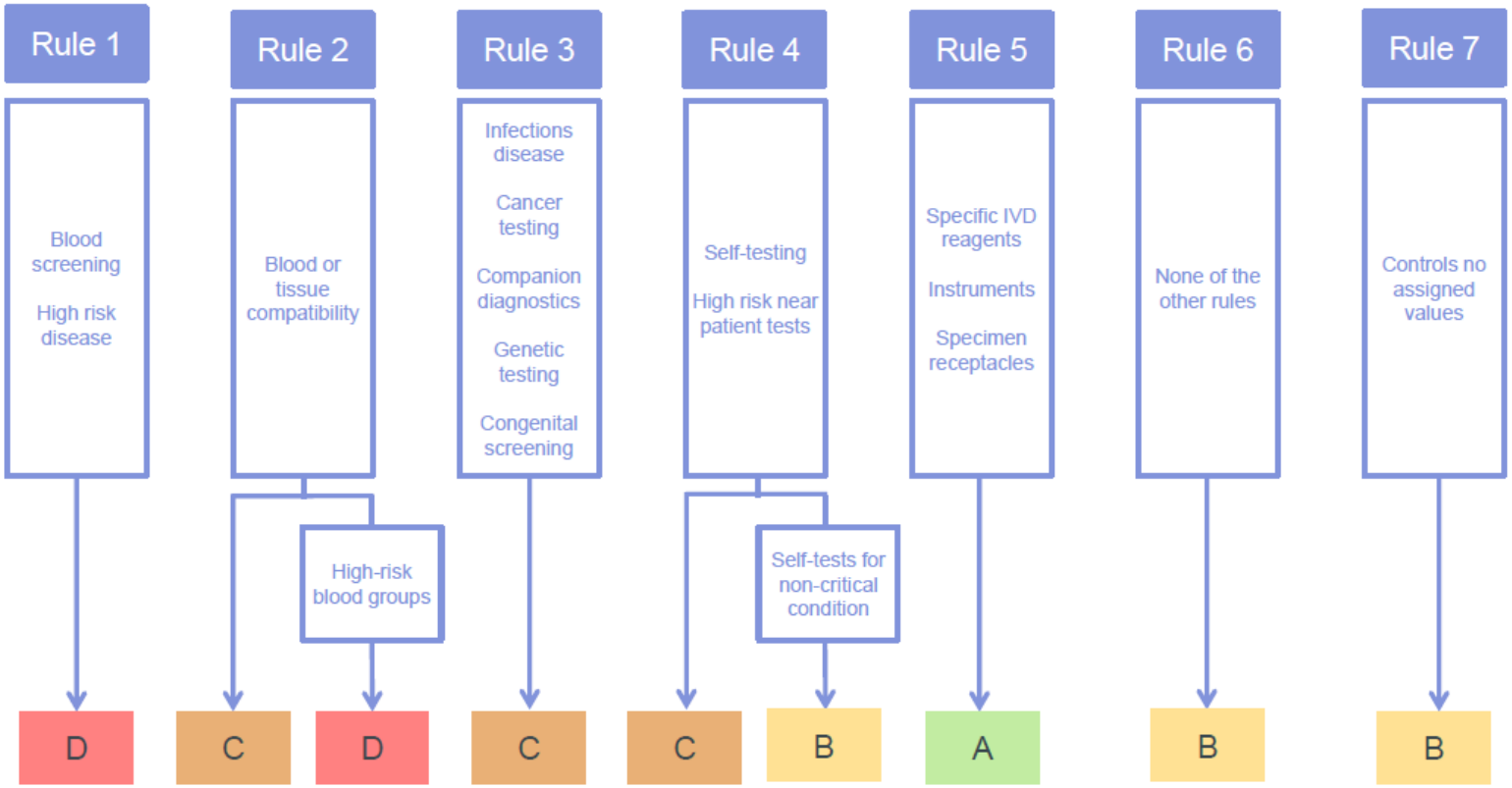
- General IVDs
- IVDs for self-testing
- Annex II List B
- Annex II List A

IVDs are not divided into classes.
Notified Bodies are only involved for self-testing IVDs and IVDs listed on the IVDD's Annex II (list A and list B)

Actually around 20% of all IVD's

	Individual Patient Risk		Public Health Risk
Class A	Low	AND	Low
	Examples: clinical chemistry analyser, prepared selective culture		
Class B	Moderate	AND/OR	Low
	Examples: Pregnancy self testing, urine test strips, vitamin B12 test		
Class C	High	AND/OR	Moderate
	Examples: Blood glucose self testing, HPV screening, Rubella test, Companion diagnostic test		
Class D	High	AND	High
	Examples: HIV blood donor screening, Ebola blood diagnostic		

EU medical devices regulations – Classification (IVDR)



Performance evaluation, performance studies and clinical evidence

- The performance evaluation shall be thorough and objective, considering both **favourable and unfavourable data**.
- A **performance evaluation plan** shall include:
  - intended purpose
  - specification of the characteristics
  - a specification of the analyte of marker to be determined
  - identification of the reference materials
  - clear identification of the specified target patient groups
  - general safety and performance requirements
  - specification and limitations of the methods
  - software
- Demonstration of the:
  analytical performance – clinical performance – clinical utility

EU IVD Regulation: Definition and general rules
Chapter II, Article 5: In-house tests/lab-developed tests

- An in-house test is an IVD that is **'manufactured and used within a health institution'**
- All IVDs that are put on the market or into service (incl. IHTs) must comply with the IVDR (General Safety and Performance Requirements of Annex I)
- IHTs are **not exempted from the requirements in the IVDR**
- Unless they are manufactured 'on an industrial scale'
- The device may **not be transferred to another legal entity**
- **Justify that patient needs are not met by available tests**
- Health Institution needs to give transparency by **publishing a declaration** (e.g. on compliance with the general safety and performance requirements)
- For population screening programs IHTs won't be allowed

Conclusion

The four pillars of the EU IVD Regulation

- **Patient safety:** High level of human health and safety
- **Free & fair trade:** Free movement & smooth functioning of IVDs in the EU
- **Harmonisation:** The EU IVDR is applicable to al Member States across the EU
  From 20% classification → > 80%
- **Innovation:** Many provisions to the latest evolutions in the sector (CDx, apps)

- Federal Agency for Medicines and Health Products is the competent authority for Belgium responsible for the EU IVDR
- Actual impact on Health Institutions and Industry is unknown

Doing now what patients need next