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European Regulatory Services

EU Regulation 2017/746 on In Vitro Diagnostic Medical Devices (IVDR)

NVKFAZ Lustrumsymposium

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Overview

IVDR

- **General Aspects of the IVDR**
- Laboratory-Developed Tests under the IVDR
- IVDR Timelines

IVDR = EU IVD-Regulation 2017/746

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

CE IVD

- **Past** = CE-marked IVD Devices on EU Market under **IVD Directive (IVDD)**
- **Future** = CE-marked IVD Devices on EU Market under **IVD Regulation (IVDR)**
- **Today** = **Transition Period**
  - IVDR went into force on 26-MAY-2017
  - But CE-marked IVD devices, certified under IVDD, can still be put on the EU Market

Scope of IVDR Regulation

- In Vitro Diagnostic (IVD) devices/assays
- Accessories
- Specimen Receptacles
- Devices for Performance Evaluation
- **Laboratory-Developed Tests (LDT)**
- Diagnostic Test services
- Internet sales / distant sales

NOT in Scope of IVDR Regulation

- **General Laboratory Products & Equipment**
- **RUO-labelled products**
- IVD for forensic or veterinary use
- Invasive sampling devices
- International certified reference materials
- **Materials for EQAS**
- IVD incorporating a Medical Device
  - Regulated as a medical device but Annex I of IVDR applies

What is an In Vitro Diagnostic?

- '*in vitro diagnostic medical device*' means **any medical device** which is a
  - reagent
  - reagent product
  - calibrator
  - control material
  - kit
  - instrument
  - apparatus
  - 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** :…*

...

- *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, or*
- *to determine the safety and compatibility with potential recepients, or*
- *to predict treatment response or reactions, or*
- *to monitor therapeutic measures. "*

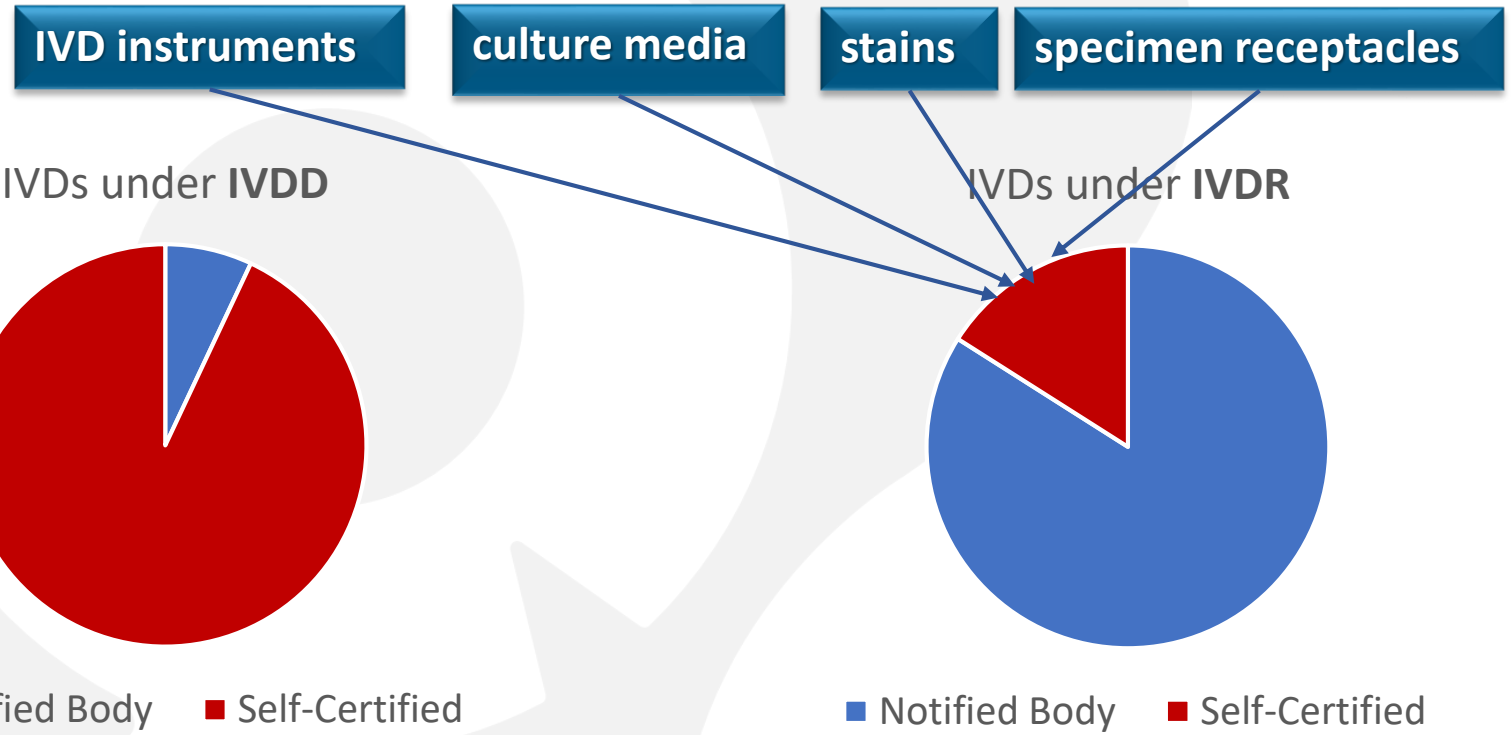
IVD Directive versus IVD Regulation

- Vast majority of IVDs are **self-certified**
  - Process for self-certification of products is relatively fast and easy = easy access to EU market
  - No need to contract (pay) a Notified Body
- Relatively easy approach to generate performance evaluation data
  - Data essentially limited to **Analytical Performance**
- 2 categories: professional use / self-test
- 3 Classes of IVDs

- Vast majority of IVDs will be under **Notified Body review/approval**
  - Complex and costly process = more complex access to EU market
  - Need to contract (pay) a Notified Body
- More complex & costly approach to generate **Clinical Evidence data**
  - Analytical Performance, Clinical Performance, Scientific Validity
- 4 categories: professional use, Near-Patient Test (POC), self-tests, CoDx.
- 4 Classes, based on risk for patient and public health

IVDR: The end of the Self-Certification Era

- Under the IVDR, an estimated 84% of the IVDs need to be certified by a Notified Body compared to only 7% under the IVDD*



* van Drongelen A, de Bruijn A, Pennings J, van der Maaden T. The impact of the new European IVD classification rules on the notified body involvement. A study on the IVDs registered in the Netherlands. RIVM Letter report 2018-0082

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Laboratory-Developed Tests (LDT)

- Laboratory-developed tests = LDTs = “home brew” tests
  - “*an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory*.” FDA
- Not strictly defined in IVDR, but can be identified as either*:
  - Tests based on a published method
  - RUO tests: Products with a clear diagnostic intended purpose but limited for Research Use Only
  - Off-label combination of CE-marked IVDs
  - Off-label sample preparation for CE-marked IVDs
  - Off-label modifications/changes of reagent, reference and calibration materials and/or equipment which are normally CE-marked IVDs

* De Bruijn ACP, Roszek BR. In-huis ontwikkelde IVD testen: gebruik en kwaliteitsborging. Rijksinstituut voor Volksgezondheid en Milieu. RIVM Briefrapport 2015-0152

Laboratory-Developed Tests (LDT)

- Today, a substantial part of IVD testing done is done using products/technologies that are **not included in the scope of the IVDD**
  - Although a large majority of **lab results** are generated with a CE-marked IVD, a substantial amount of **lab tests** are not CE-marked IVD methods*:
  - **“True” LDTs**: done by the labs because there are no equivalent tests on the market, or
  - **RUO** and **Off-Label CE-IVD** Tests: done by the labs to improve laboratory workflow and/or to reduce costs.

* Vermeersch et al.: New IVD Regulation 2017/746: impact on a large University hospital. Clin Chem Lab Med 2020

Laboratory-Developed Tests (LDT)

- IVDR explicitly recognizes the need for self-developed tests…
  - "*Health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, on a non-industrial scale, the specific needs of* ***target patient groups which cannot be met at the appropriate level of performance by an equivalent device*** *available on the market*"

- … But regulates their use through Article 5, essentially aiming to **restrict the use of this second category of LDTs**.

"True LDTs"

IVDR Art. 5: "Placing on the market and putting into service"

- **IVDR Art. 5.1**: A device may be placed on the market or put into service **only** if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose.

- **IVDR Art. 5.4**: Devices that are **manufactured and used within health institutions**,(…) shall be considered as having been put into service.
  - "health institution" means an organization the primary purpose of which is the care or treatment of patients or the promotion of public health.

This means: "Clinical Labs"

- 5.1 + 5.4 = **LDTs are in the scope of the IVDR** !

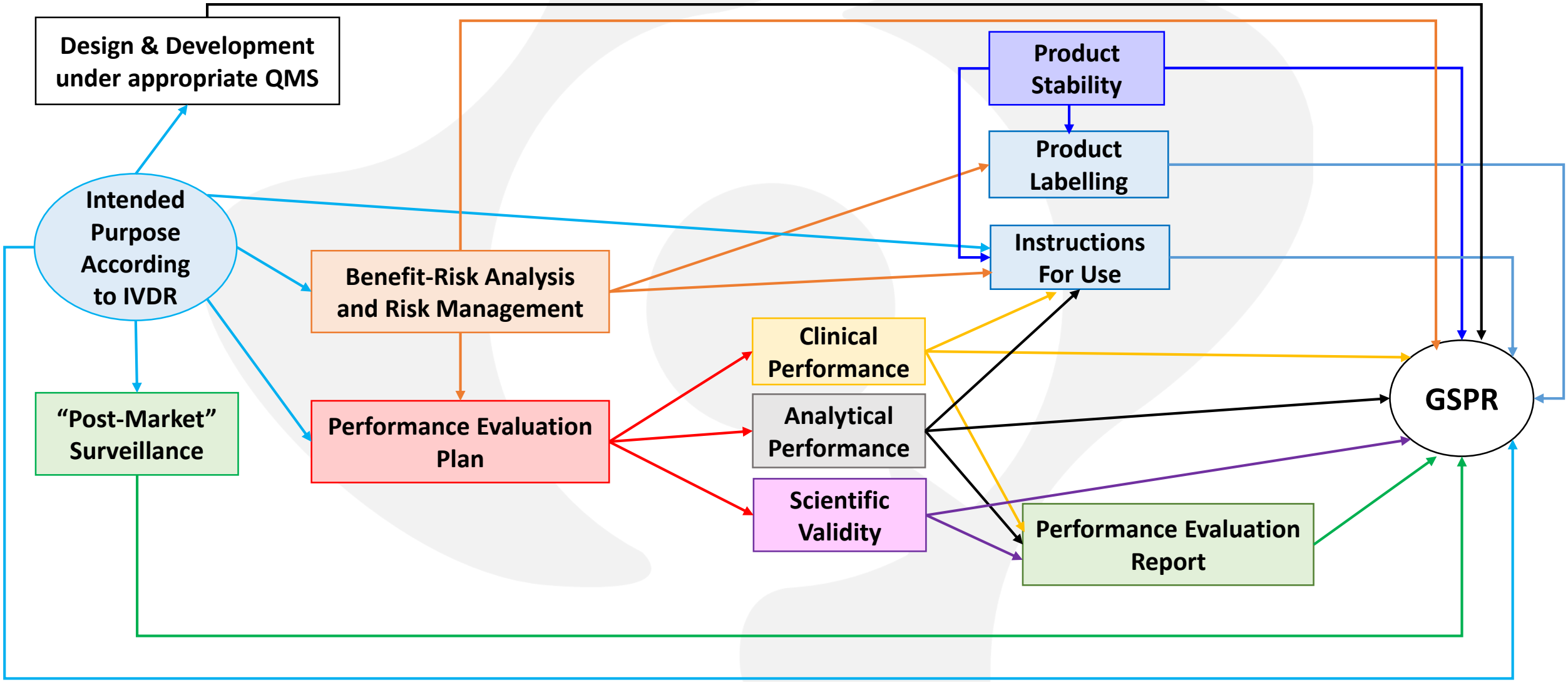
IVDR Art. 5: "Placing on the market and putting into service"

- **IVDR Art. 5.5**: specifies that the IVD-R does not *fully* apply to devices manufactured and used within clinical laboratories provided that:
  - devices are manufactured and used ONLY within EU Health Institutions
  - devices are not transferred to other legal entities
  - are not made on an industrial scale

  - lab must make LDT under appropriate QMS for manufacturing of medical devices
  - lab must be compliant to EN ISO 15189 (or applicable national provisions incl. accreditation)

  - lab must provide documented justification that **no commercially available device has the appropriate level of performance** to meet the target patient group's specific needs
  - lab must draw up a declaration that the LDT meets all relevant IVDR Annex I **General Safety & Performance Requirements** (GSPR)
  - lab reviews **experience gained from clinical use** of the devices and takes all necessary corrective actions ("post-market surveillance")

IVDR Art. 5.5 is not a free pass for “True” LDTs



IVDR Art. 5.5 is not a free pass for "True" LDTs

ISO 15189:2007
Medical laboratories

14971
Risk Management

ISO 13485:2016

EUROPEAN STANDARD
NORME EUROPÉENNE
EUROPÄISCHE NORM

EN 13612

March 2002

ICS 11.100

English version

Performance evaluation of in vitro diagnostic medical devices

Who will be responsible to enforce IVDR Art. 5 ?

- The **National Competent Authorities (CA)** of each EU Member State are responsible to enforce Art. 5

- Several of them are already structuring themselves to carry out this task

- In general, the CA are expected to challenge on the use of LDTs to deliver patient-impacting results
  - Maybe different degrees of enforcement varying from Member State to Member State

Impact of IVDR Art. 5 on the clinical laboratory

- If a clinical lab truly wants to continue using an own LDT, it has to be ready to defend its position in front of its own CA, **and still comply with all Art. 5.5 requirements**
  - “Compliance with the IVDR will require a major investment of time and effort”*
- As a result, labs will be strongly pushed to use CE-marked IVDs if possible
- But it is currently not clear to which extent the use of CE-marked IVD with “minor” modifications of the Instructions for Use will be seen as LDT

* Vermeersch et al.: New IVD Regulation 2017/746: impact on a large University hospital. Clin Chem Lab Med 2020

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Full Applicability of IVDR Will Be Delayed

- Original Timeline
  - Full Applicability as of **26-MAY-2022**
  - Sell-off period for IVDD devices already placed on the EU market until **26-MAY-2025**

- But on 25-JAN-2022, new timelines were adopted (transitional provisions)

REGULATION (EU) 2022/112 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 January 2022

amending Regulation (EU) 2017/746 as regards transitional provisions for certain *in vitro* diagnostic medical devices and the deferred application of conditions for in-house devices

Proposed Timeline – Certification of IVDs under IVDR

Classification Under		Proposal		
IVD Directive	IVD Regulation	Transitional Provision	Sell-off Provision	Conditions
Never released under IVDD	All classes	None (26-MAY-2022)		None
Annex II List A	Class C or D	Expiry date certificate or 26-MAY-2025	26-MAY-2025	Valid Notified Body Certificate, no significant changes in design, post-market surveillance, vigilance, registration of economic operators and of devices according to IVDR
Annex II List B	Class C or D			
Self-Testing Devices	Class B, C or D			
Self-Certified	Class A	None (26-MAY-2022)	26-MAY-2025	Declaration of Conformity drawn up prior to 26-MAY-2022, no significant changes in design, post-market surveillance, vigilance, registration of economic operators and of devices according to IVDR
	Class A sterile	26-MAY-2027	26-MAY-2028	
	Class B	26-MAY-2027	26-MAY-2028	
	Class C	26-MAY-2026	26-MAY-2027	
	Class D	26-MAY-2025	26-MAY-2026	

Proposed Timeline – Obligations under Art. 5.5 (LDTs)

- Obligation, applicable as of **26-MAY-2022**:
  - 5.5(a) lab must not transfer device to other legal entity

- Obligation, applicable as of **26-MAY-2024**:
  - 5.5(b) lab must make LDT under appropriate QMS
  - 5.5(c) lab must be compliant to ISO 15189
  - 5.5(e) lab provides info to own CA on the use of LDT including justification of manufacturing/modification/use
  - 5.5(f) lab must draw up a declaration for its own LDT including name & address, device identification declaration that devices meets relevant GSPR
  - 5.5(g) special requirements for Class D LDTs
  - 5.5(i) lab implements PMS

- Obligation, applicable as of **26-MAY-2028**:
  - 5.5(d) lab must provide justification that no commercially available device is equivalent to its LDT

Thank you for listening!

Do you have any questions?

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