EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Update on the roll out of the In Vitro Diagnostic Medical Devices Regulation 2017/746 (IVDR)

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EQALM symposium, 12 October 2022

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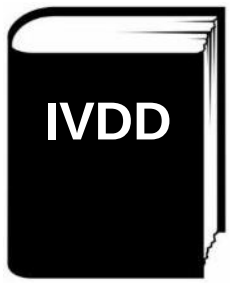
I. Rationale for the IVD Regulation

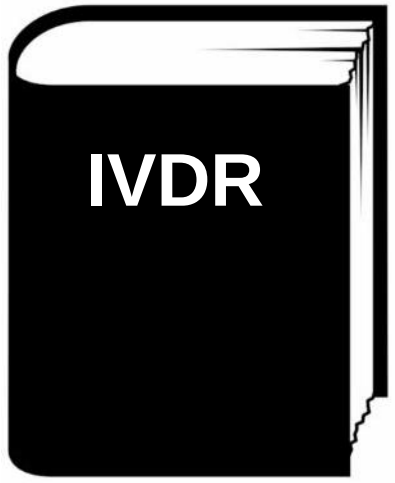
The purpose of IVDR legislation is to **regulate the trade in IVDs in the EU** and, and by doing so, to guarantee the **safety, suitability and performance** as well as safeguard the **health** and ensure the necessary **protection** of patients, users and other persons.

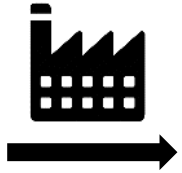
Since 26 May 2022: from IVDD to IVDR

- IVD**D** regulates commercial IVDs (CE-IVDs)
- IVD**R** regulates CE-IVDs and In House-IVDs (LDTs)

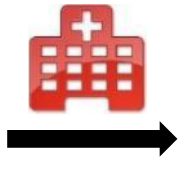


1998 - 2022





CE-IVDs



LDTs

Laboratory-developed tests / In-house devices

Entry into force: 2017

5 years for Implementation

Date of application: May 26th, 2022

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Slide from Van Dongen, 9th ESLHO Symposium, Zoom webinar, 5 November 2020

Structure of the IVDR and recommended reading 1/2

IVDR part	Number	Title	Recommended reading *(Parts indicated in red apply to IH-IVDs)*
Why? Preambles	1-101	NA	**Preamble 1-2, 28-29, 61-63, 75, 77**
What? Chapters	I	Introductory provisions	**Art. 1**
	II	Making available on the market, and putting into service of devices, obligations of economic operators, CE marking, free movement	**Art. 2 (definitions), 5*, 10**
	III	Identification and traceability of devices, registration of devices and economic operators, summary of safety and clinical performance, European database on medical devices	**Art. 29**
	IV	Notified bodies	-
	V	Classification and conformity assessment	**Art. 47***
	VI	Clinical evidence, performance evaluation and performance studies	**Art. 56-58***
	VII	Post-market surveillance, vigilance and market surveillance	**Art. 78*, 82**
	VIII	Cooperation between member states, medical device coordination group, EU reference laboratories and device registers	**Art. 96-100**
	IX	Confidentiality, data protection, funding and penalties	-
	X	Final provisions	**Art. 110**

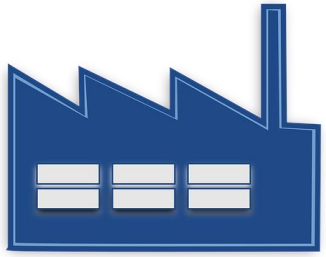
Lubbers et al., Hemasphere 2021; 5:5(e568).

Structure of the IVDR and recommended reading 2/2

How? Annexes	I	General safety and performance requirements	**All sections**
	II	Technical documentation	**All sections**
	III	Technical documentation on post-market surveillance	**All sections**
	IV	EU declaration of conformity	-
	V	CE marking of conformity	-
	VI	Information to be submitted upon the registration of devices and economic operators	-
	VII	Requirements to be met by notified bodies	-
	VIII	Classification rules	**All sections**
	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	**All sections**
	XIV	Interventional clinical studies and certain other performance studies	-
	XV	Correlation table (with the IVDD)	-

Lubbers et al., Hemasphere 2021; 5:5(e568).

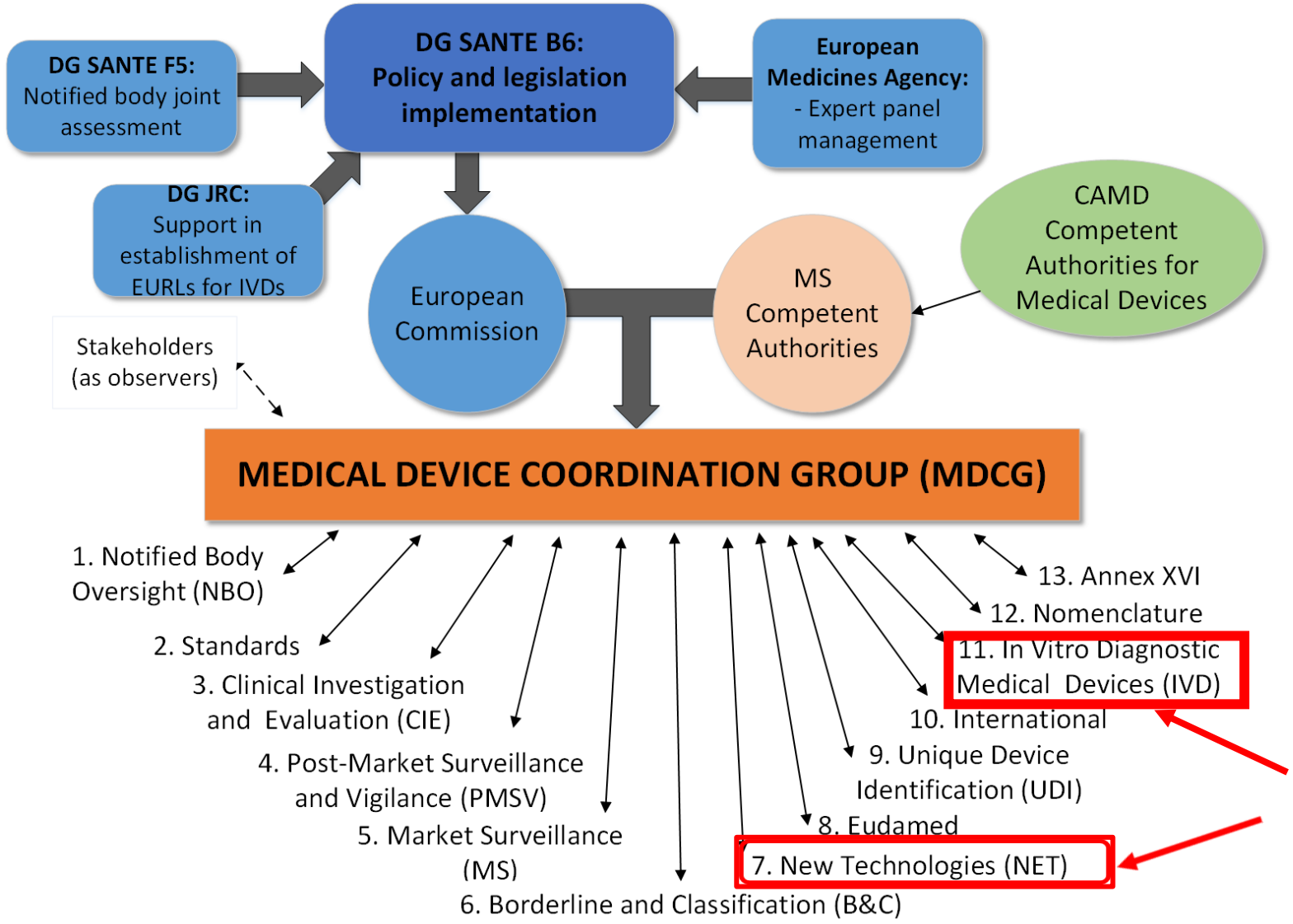
Areas of the regulatory framework



Pre-market → Post-market

Pre-market	Post-market
Qualification/ classification	Post-market surveillance (manufacturer)
Conformity assessment	Market surveillance (competent authorities)
Performance evaluation/ performance study	Vigilance

Governance of EU-level implementation



European Commission

Who is in the IVD WG < MDCG?

- **Terms of Reference**: https://ec.europa.eu/health/sites/default/files/md_dialogue/docs/md_tor_wg11_ivd_en.pdf
- **Members**: EU competent authorities from the 27 Member States
- **Observers**: IS, NO, LI, TU
- **Observers**: BioMed Alliance, European Association of Authorised Representatives (EAAR), European Federation of Laboratory Medicine (EFLM), MedTech Europe, notified bodies - Team-NB, NB-Med, European Federation of Pharmaceutical Industries and Associations (EFPIA)
- **Link to agencies**: ECDC (to be developed further), EMA

II. IVDR KEY CHANGES

The EU IVDD has been revised and strengthened in the IVD Regulation

L 117/176 EN Official Journal of the European Union 5.5.2017

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

(Text with EEA relevance)

Key changes:

- **Risk-based test classification**
- **Clinical evidence requirements**
- **Notified body assessment**
- Expert panel advice & EURL
- EUDAMED database
- UDI
- **CE-IVDs versus IH-IVDs (exempted!)**

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IVDR: Opportunities & Threats

1. Scope enlargement & (Re)Classification
2. Clinical Evidence Requirements

Opportunities

3. Notified bodies and Conformity Assessment**

   for ~ 85% of commercial tests (classes A sterile, B, C, D);

Threats!?

4. "In house" developed tests: an exemption that comes with obligations!

   Art 5.5 compliance needed; address carefully art 5.5.d. regarding equivalence of tests

5. Increased cost!?

****PREPAREDNESS OF MEDICAL LAB SECTOR IS FOR COMMERCIAL TESTS FULLY DEPENDENT ON TIMELY TEST CERTIFICATION THROUGH EU REGULATORY SYSTEM, AS INTENDED IN THE IVDR (NOTIFIED BODIES, EXPERT PANELS, REFERENCE LABS, GUIDANCE DOCUMENTS, ….).**

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Redefinition of an IVD medical device

In Vitro Diagnostic MD

- ...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...to be used *in vitro* for the examination of specimens, including blood and tissue donations... from the human body,
- solely or principally for...providing information..

Note that tangible products/ kits are regulated by the IVDR, not pathology services.

Scope Enlargement

... solely or principally for the purpose of providing information on one or more of the fo ing:

(a) Concerning a physiologic ess of state;
(b) Concerning congenital physical or
(c) Concerning the predisposition to a medical co a disease;
(d) To determine the safety an compatibility with potential recipients;
(e) To predict treatment respo se or reactions;
(f) To define or monitor therap eutic measures.

SCOPE ENLARGEMENT
Including high risk "In House" tests

Companion Diagnostics

Genetic testing

Test (Re)Classification

- Major changes to how IVDs are classified.
- Will be a **RISK-RULE BASED SYSTEM** using Global Harmonisation Task Force (GHTF) classification rules.
- Impacts most IVD manufacturers and **80-90% of tests**: quantum leap!
- Classification depends upon **THE INTENDED USE AND THE LEVEL OF RISK TO THE PATIENT AND THE PUBLIC** (taking into account the likelihood of harm and the severity of that harm).
- Identical devices may be classified differently if they are to be used for different diagnostic purposes. This is why the manufacturer's intended use of the device is critical to determining the appropriate class.

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Risk-based classification system for medical tests under the IVDR 2017/746

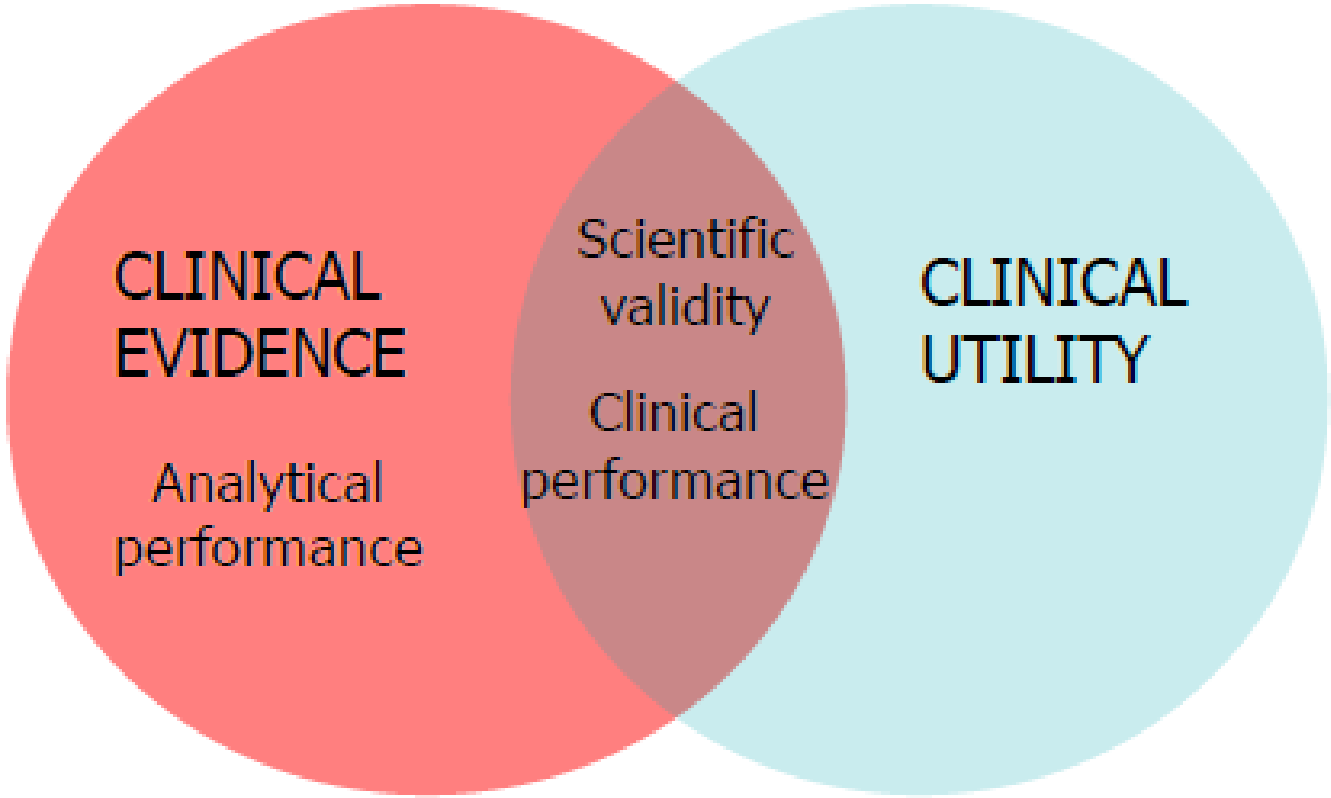
D	▪ High public health risk ▪ Blood safety / high risk infectious diseases
C	▪ High risk for individual patients ▪ E.g. cancer markers, dangerous infectious diseases, etc.
B	▪ Medium risk for individual patients ▪ E.g. blood chemistry, pregnancy tests, etc.
A	▪ Low risk for individual patients ▪ Instruments, accessories, specimen collection systems etc.

CCLM 2021, Cobbaert et al.

Clinical Evidence Requirements

NEW REQUIREMENT WITH MAJOR IMPACT!

Clinical Evidence = clinical data and performance evaluation results, pertaining to a device of sufficient amount and quality **to allow a qualified assessment of whether the device achieves the intended clinical benefit and safety, when used as intended by the manufacturer.**



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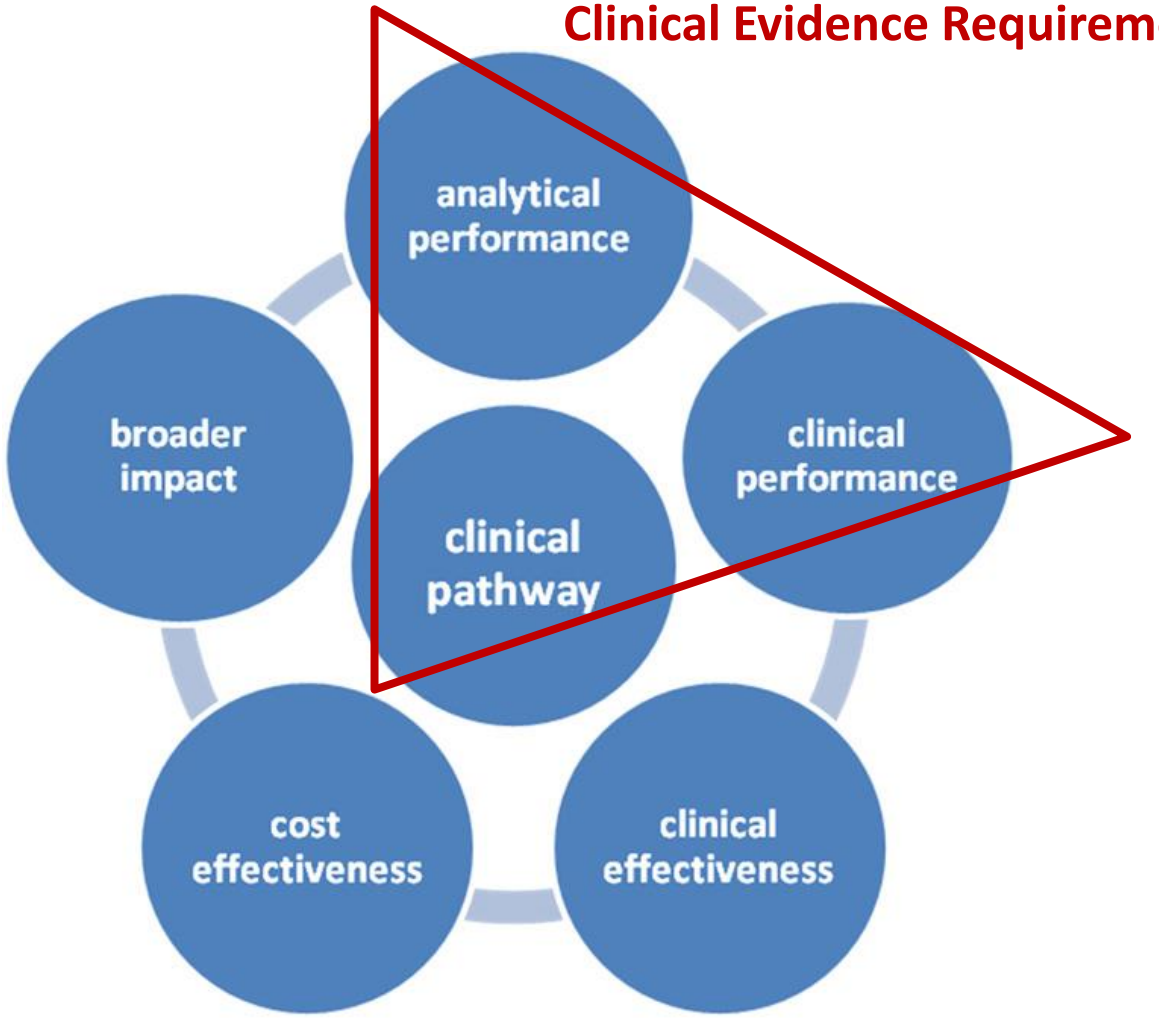
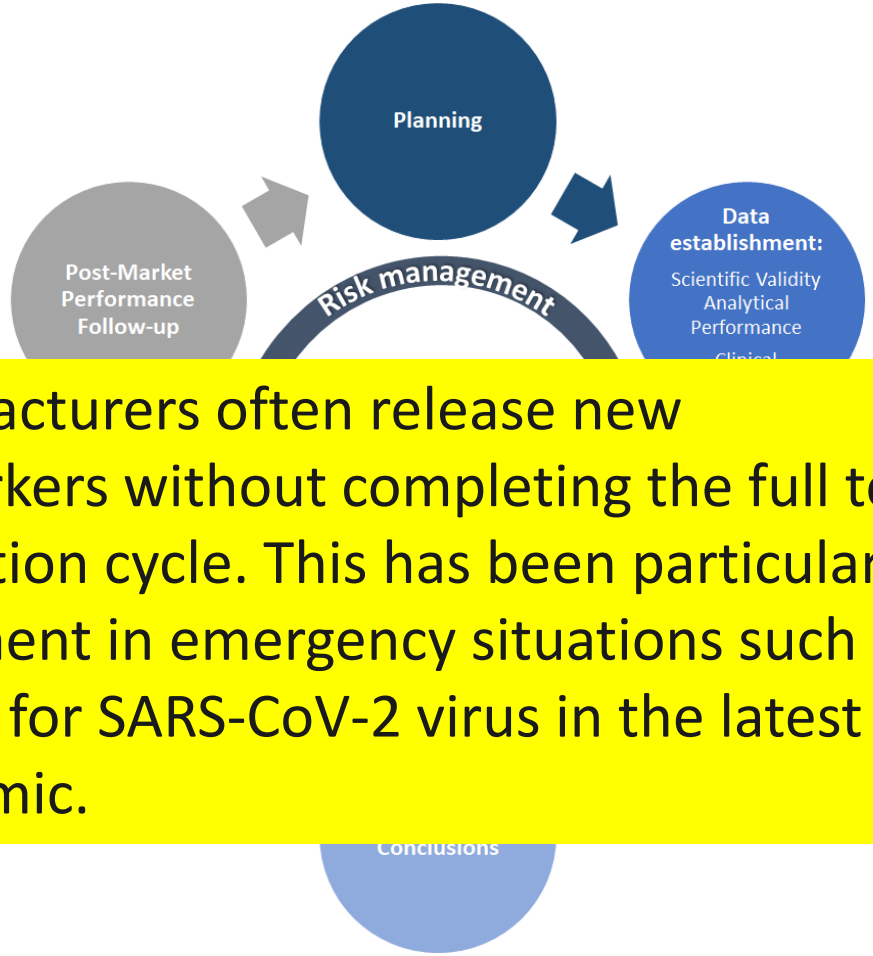
IVDR 2071/746 superposed on EFLM Test Evaluation framework





Manufacturers often release new biomarkers without completing the full test evaluation cycle. This has been particularly prominent in emergency situations such as testing for SARS-CoV-2 virus in the latest pandemic.

Medical tests should be fit-for-clinical-purpose THROUGH THEIR ENTIRE LIFE CYCLE (PEP and PMPF)!

Performance Evaluation Plan (PEP) – Recital (61)
Post-market Performance Follow-up (PMPF) – Recital (63)

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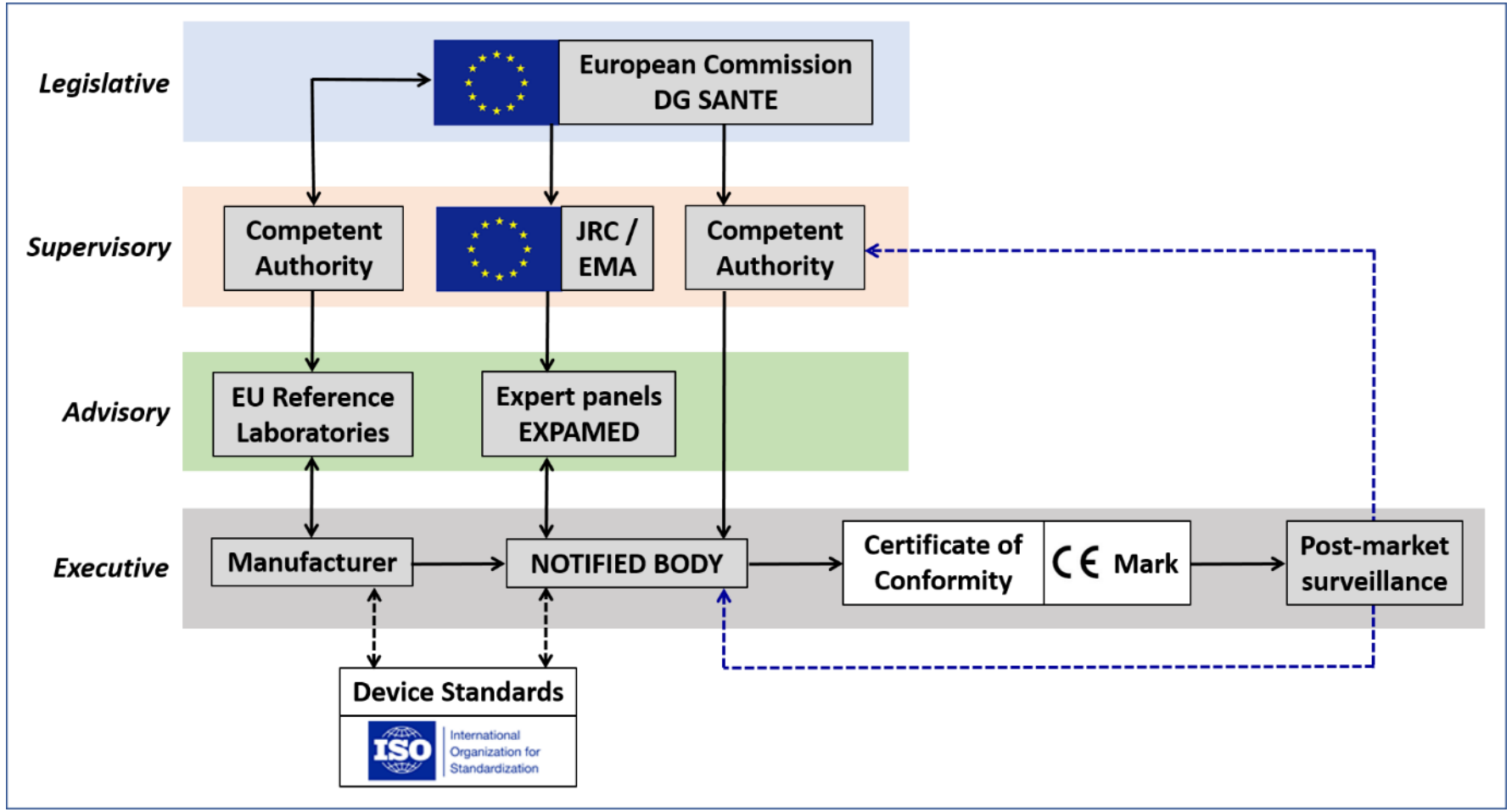
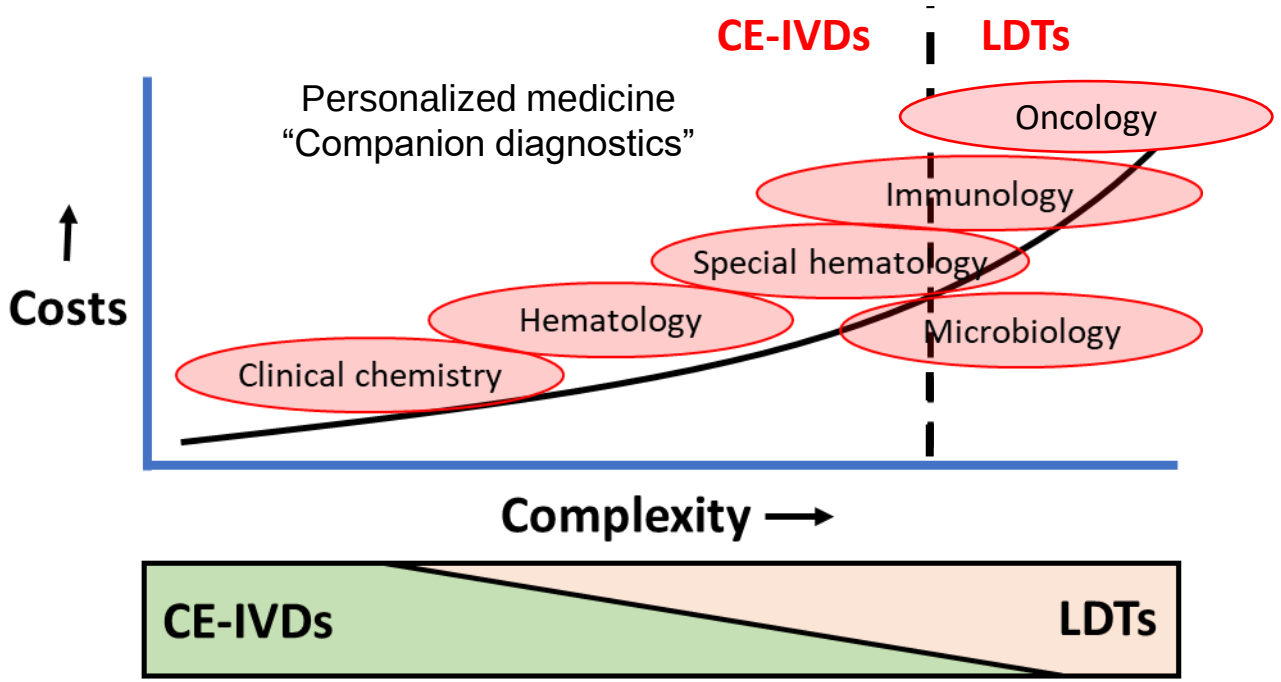
Third Party Review for 85% of medical tests:

Conformity Assessment Process of CE-IVDs under the IVDR



Cobbaert et al., CCLM 2022; 60(1): 33-43.

Running high complexity In-House Tests comes with obligations



Cellular, Protein and Molecular

Diagnostic crises
Genetics
Pathology
Personalized medicine
- Cancers
- Rare genetic disorders
- …..

Many tests, performed rarely

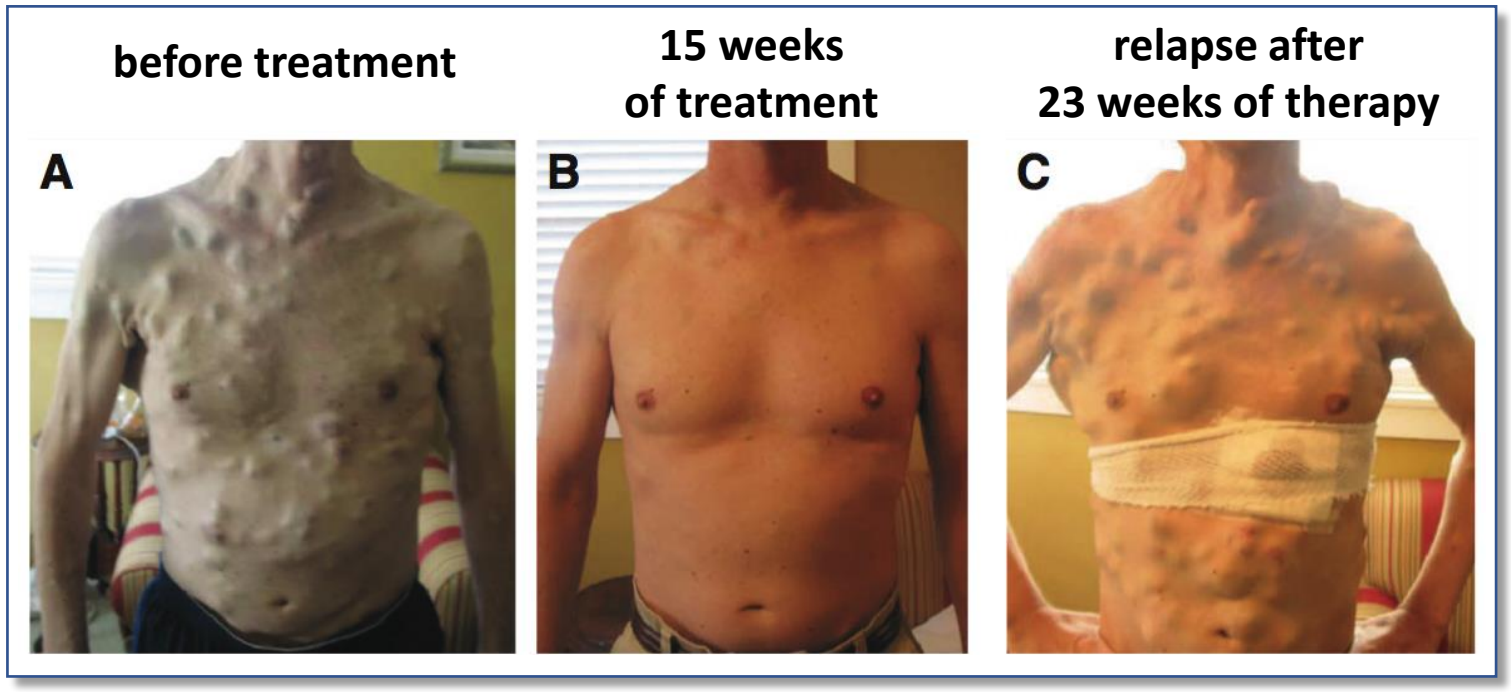
LDTs may be commercialized in case of Technology Transfer

- Assays with higher complexity are more difficult to commercialize
- To provide optimal healthcare, diagnostic laboratories depend on development of LDTs for many (complex) applications
- This dependence differs significantly per diagnostic field

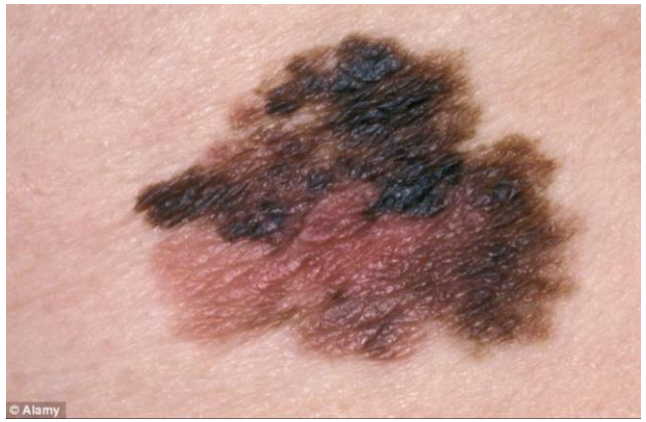
ESLHO european scientific foundation of laboratory hemato oncology

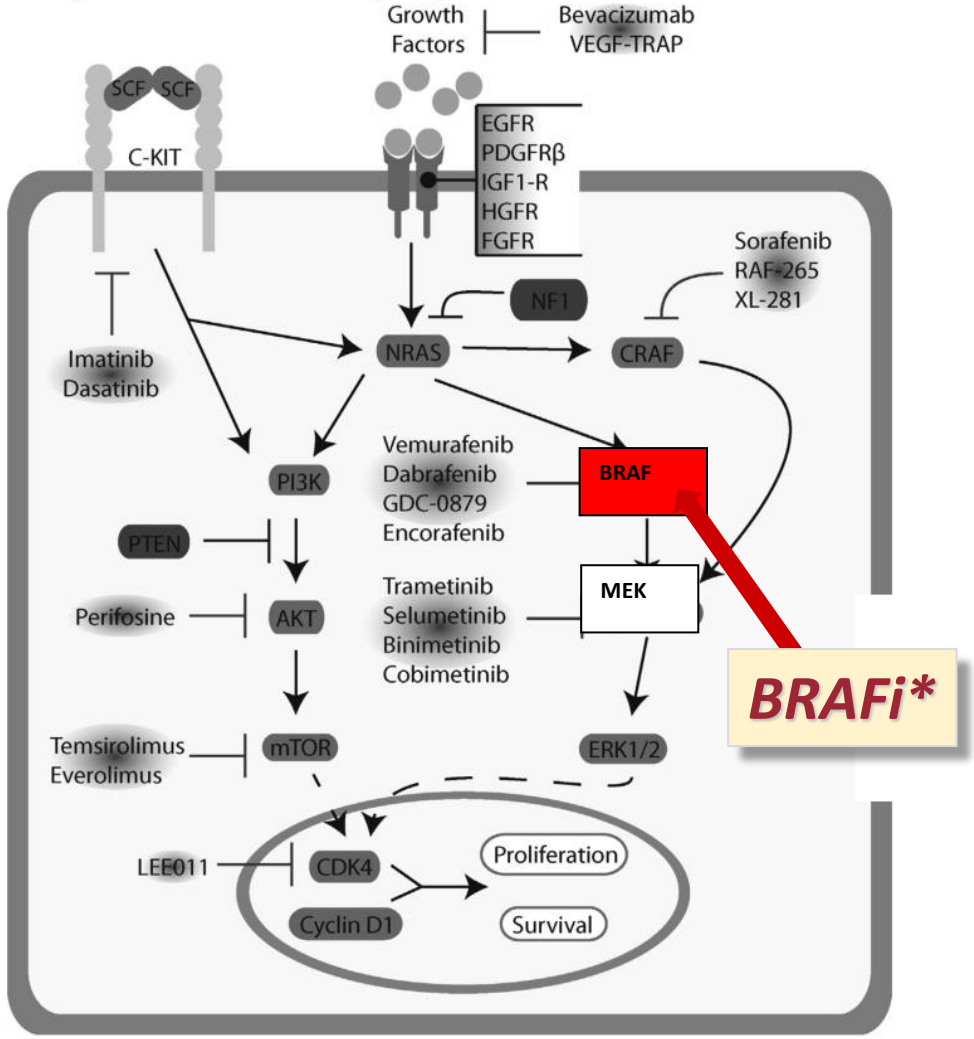
mod.: Slide from Van Dongen, 9th ESLHO Symposium, Zoom webinar, 5 November 2020

You can treat Malignant Melanoma with *BRAF* mutations (50% of cases), but tumors will develop therapy resistance



Chapman et al., **NEJM** (2012)
Hirth et al., **Nat Drug Discov** (2012)
Wagle et al., **JCO** (2011)



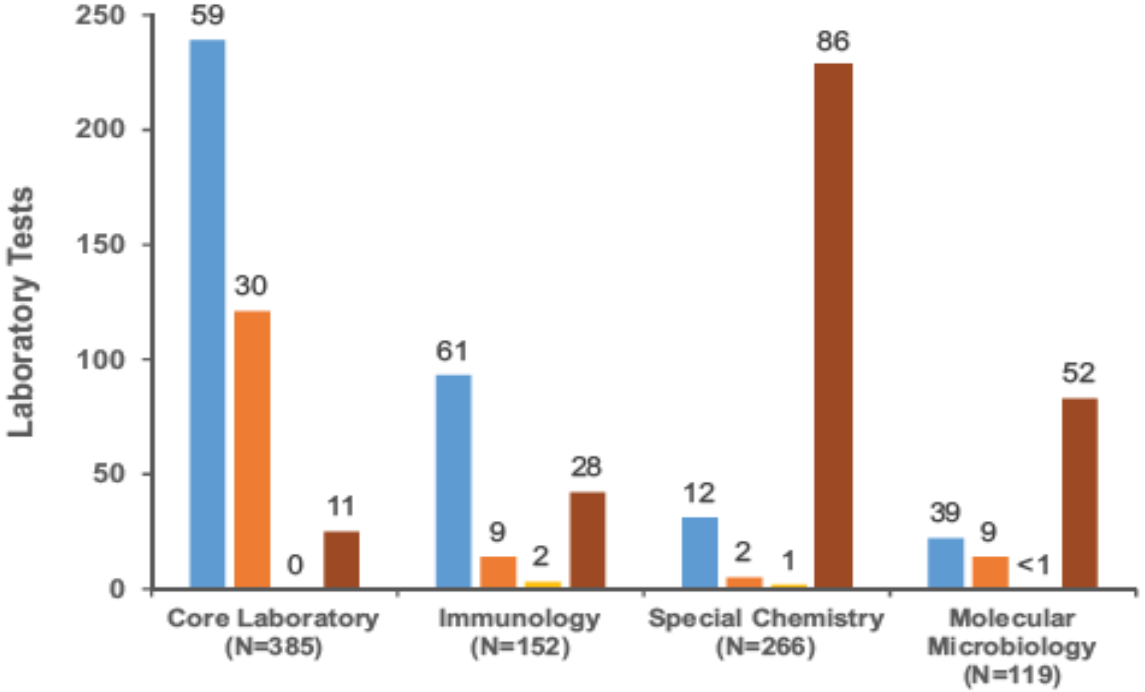


** BRAFi inhibitor therapy*

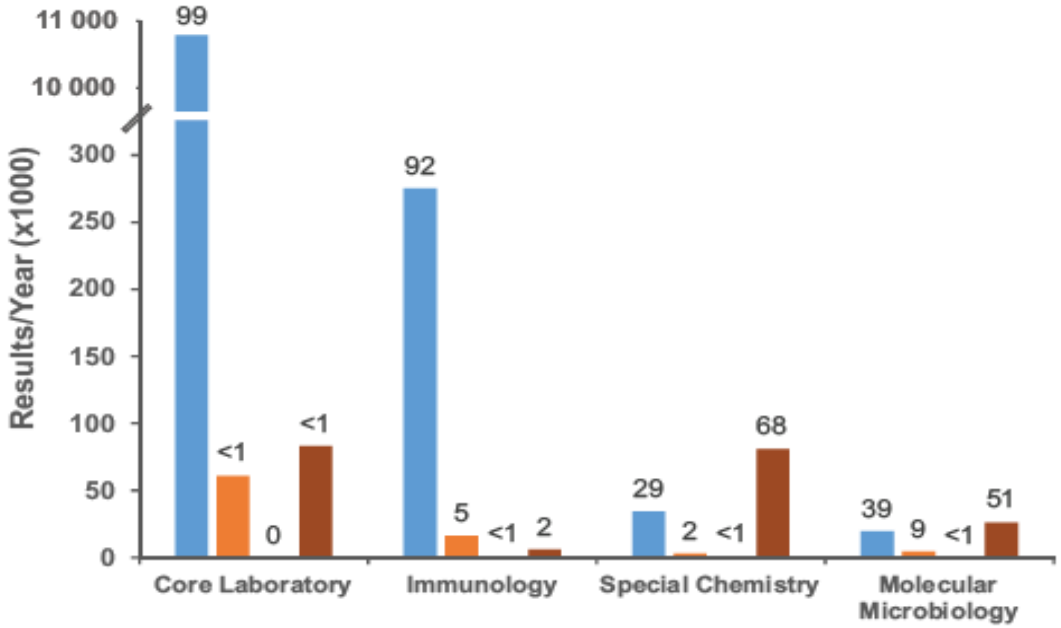
By courtesy of Prof M. Neumaier

LDTs play a Vital Role in Diagnostics

Only 42% of 922 **tests** are CE-IVDs



98% of all **results** originate from CE-IVDs



Each test was classified as Conformité Européenne (CE)-IVD, modified/off-label CE-IVD, commercial Research Use Only (RUO) or LDT. Each matrix was considered a separate test.

Vermeersch P et al., Clin Chem Lab Med 2020

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Requirements for Health Institutions with IH-IVDs (IVDR art 5.5.)

With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of the IVDR SHALL NOT APPLY to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

a. the devices are **not transferred to another legal entity**;

b. manufacture and use of the devices occur **under appropriate quality management systems**;

c. the laboratory of the health institution is **compliant with standard EN ISO 15189** or where applicable national provisions, including national provisions regarding accreditation;

d. the health institution **justifies** in its documentation that the target patient group's **specific needs cannot be met**, or cannot be met at the appropriate level of performance by an equivalent device available on the market;

e. the health institution **provides information upon request** on the use of such devices to its **competent authority**, which shall include a justification of their manufacturing, modification and use;

f. the health institution draws up **a declaration** which it shall make **publicly available**, including:

   i. the name and address of the manufacturing health institution,

   ii. the details necessary to identify the devices,

   iii. a declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefore;

Requirements for Health Institutions with IH-IVDs (IVDR art 5.5.)

g. as regards **class D devices** in accordance with the rules set out in Annex VIII, the health institution draws up documentation that makes it possible to understand the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is **sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met**. Member States may apply this provision also to class A, B, or C devices in accordance with the rules set out in Annex VIII;

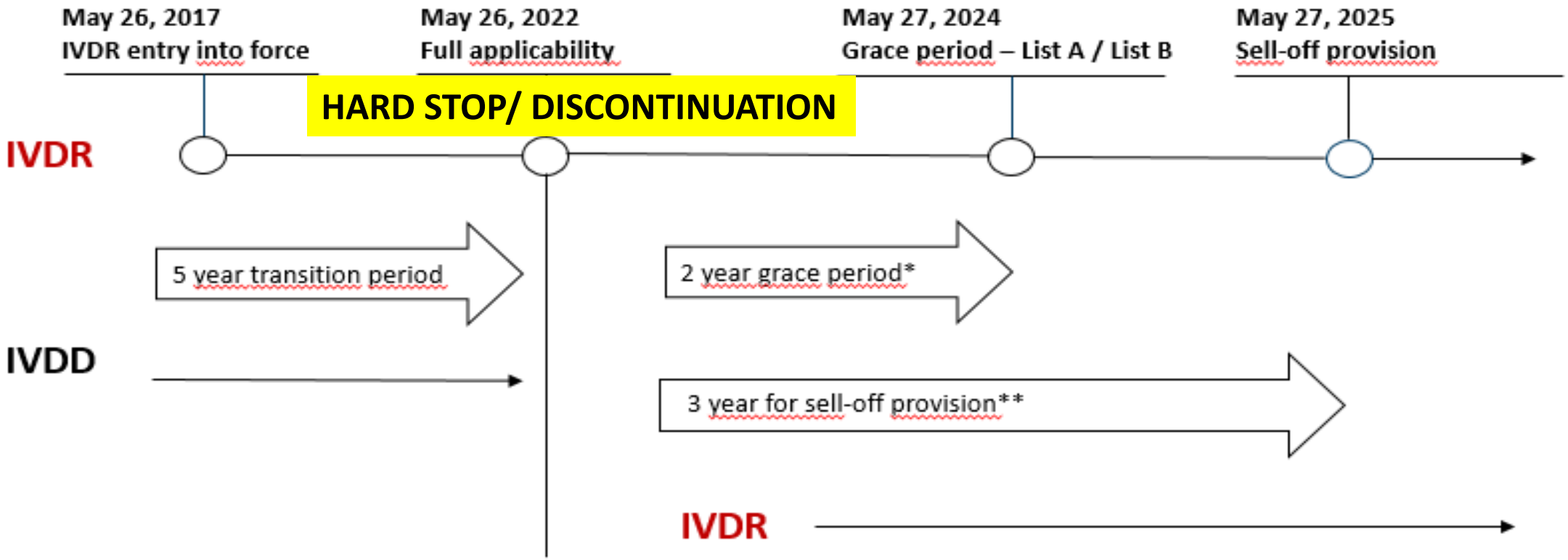
h. the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g); and

i. the health institution **reviews experience gained from clinical use** of the devices and takes all necessary corrective actions.

Member States may require that such health institutions submit to the competent authority any further relevant information about such devices which have been manufactured and used on their territory. Member States shall retain the right to restrict the manufacture and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

This paragraph shall not apply to devices that are manufactured on an industrial scale.

III. Original IVDR implementation timelines



* IVDD List A and List B devices with valid IVDD certificates can be further manufactured under specific requirements.

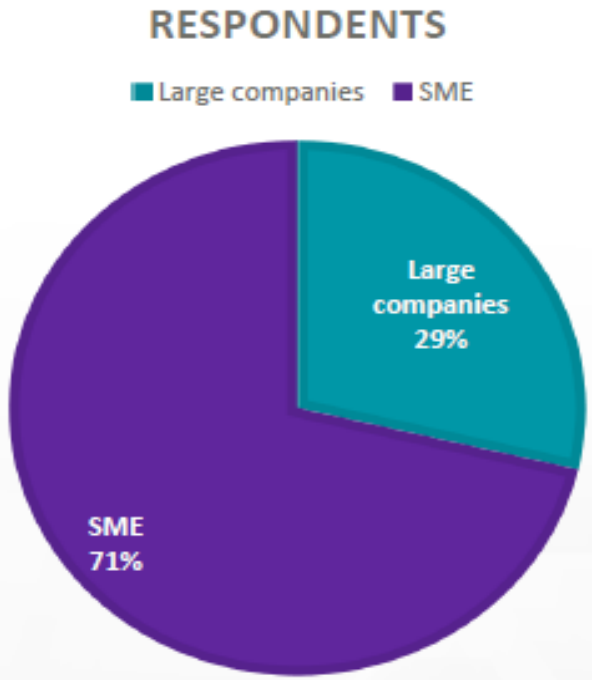
** IVDD devices which have been put in the supplier warehouses before May 26, 2022 and have not reached their final user can be sold until May 27, 2025 latest or until the expiry date is reached.

IV. CE-IVD availability: Market Survey in July 2021

Who responded to the survey?

Respondents	115* representing a rough estimated market revenue coverage of 90%**
SME	82
Large companies	33

More SMEs responded than large companies. This reflects the IVD industry in the EU.



*Compared to 65 respondents in the last survey of this type in January-February 2021

**MedTech Europe estimations based on The European IVD Market Statistics Report 2020

Market Survey in July 2021

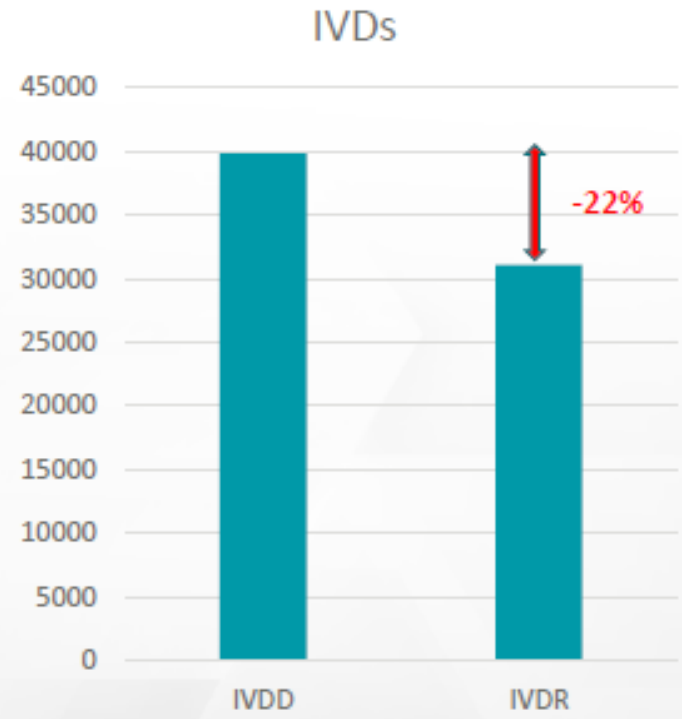
IVDs on the market under IVDD and IVDR

	IVDD	IVDR	Loss
Number of IVD devices	39.844	31.118	-8.726

The number of IVDs intended to be available to EU health services under IVDR will drop by 22%.

31.067 is the total number of devices *intended* to be CE marked under IVDR. Other data from the survey indicates that not all 31.067 IVDs will be CE marked on 26 May 2022. Therefore, a much greater disruption should be factored in for health services *see slide 10*.

See next slide for breakdown by company size



Root cause analysis of the situation?
mainly unpreparedness of the EU Regulatory Infrastructure

DE GRUYTER

Clin Chem Lab Med 2022; 60(1): 33–43

Opinion Paper

Christa Cobbaert*, Ettore D. Capoluongo, Florent J.L.A. Vanstapel, Patrick M.M. Bossuyt, Harjit Pal Bhattoa, Peter Henrik Nissen, Matthias Orth, Thomas Streichert, Ian S. Young, Elizabeth Macintyre, Alan G. Fraser and Michael Neumaier

Implementation of the new EU IVD regulation – urgent initiatives are needed to avert impending crisis

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V. Lab preparedness for LDTs?

Questionnaire, EU-wide:

203 respondents from 25 EU countries covering all diagnostic disciplines

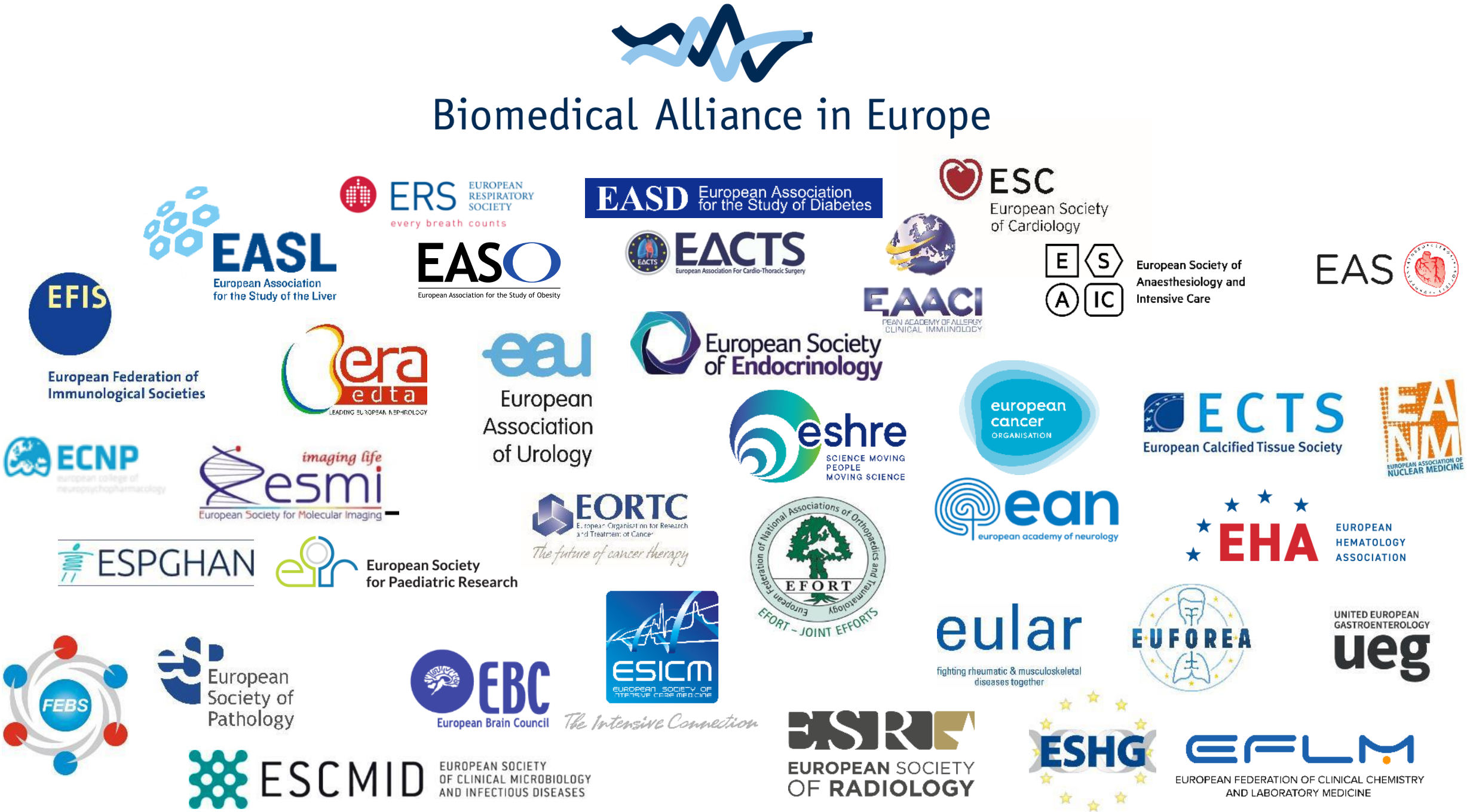
On average, one laboratory runs **99 tests** that **might need to meet the Article 5.5 requirements of the IVDR** as they are not CE-IVDs used strictly according to the instructions for use (IFU) of the manufacturer (or 77 assays if CE-IVDs with minor modifications are excluded).

Source: BioMed Alliance in Europe Survey, December 2021

Main Findings IVDR Questionnaire BioMed Alliance. 2021. Available at: https://www.biomedeurope.org/images/news/2021/20211206.Findings_IVDR_Questionnaire_final.pdf.

Dombrink et al., Hemasphere, (2022) 6:6(e724).

Biomedical Alliance in Europe



Main BMA activities in 2021

April 2021: EC STOA Workshop on the IVDR and its consequences for the EU health sector: system not in place (eg EUDAMED), loss of CE-marked kits, threats to in-house / laboratory developed tests (IHD/LDTs)…..

July to Sept. 2021: Launch of the IVDR questionnaire on preparedness of medical labs

September 2021: High-level meeting with the European Commission (DG Santé) to prevent diagnostic collapse and discuss IVDR postponement

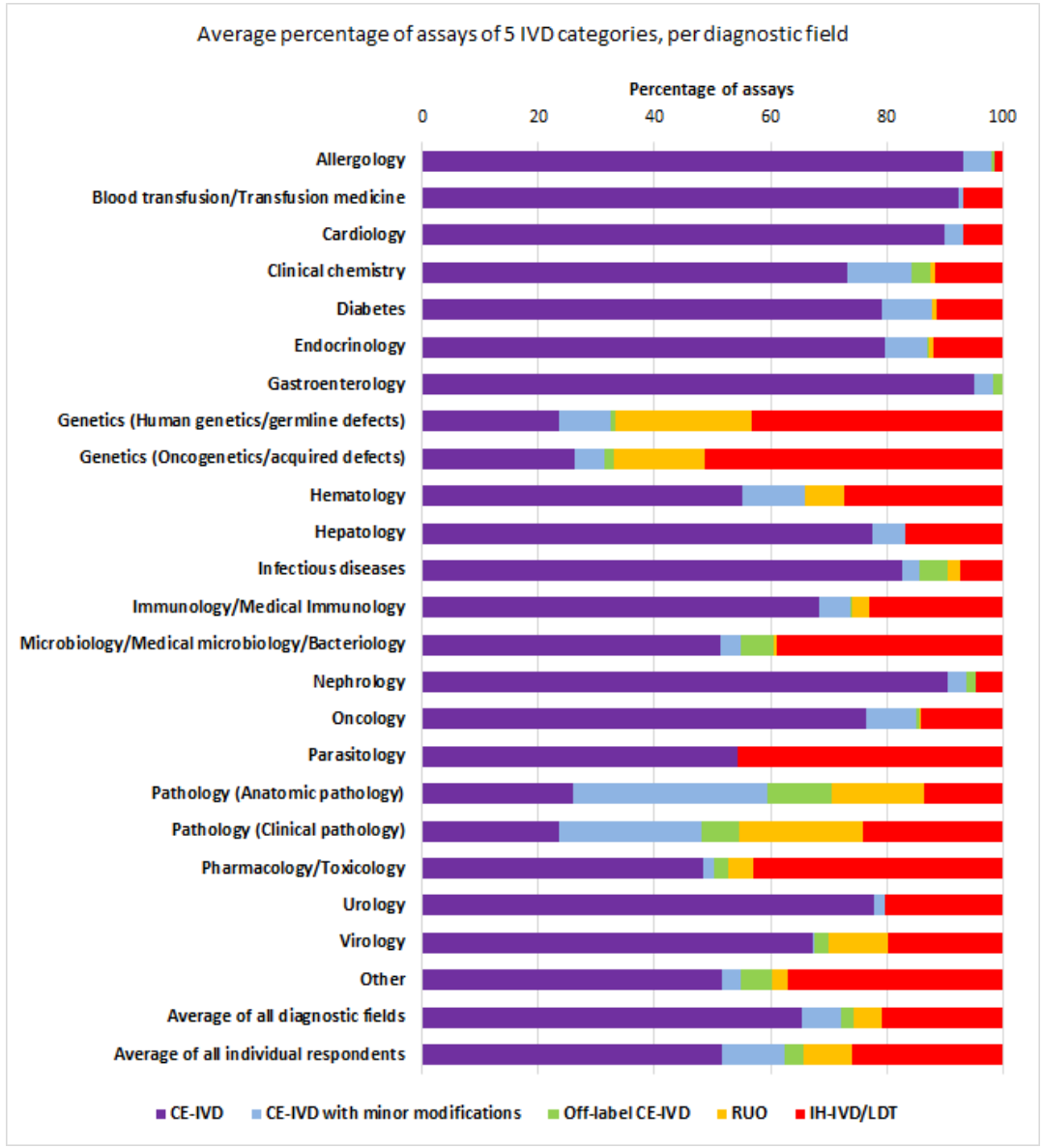
October 2021: Welcoming the amending act and extended transitional provisions. As a result of the BioMed Alliance and EFLM advocacy efforts, extended provisions are provided for in-house devices as well (Art. 5.5).

November 2021: BioMed Alliance input on the draft guidance on in-house tests. "*IVDR and NCA dictate what we must do but diagnostic specialists must define and accompany how we do it*"

November 2021: Promoting the IVDR questionnaire findings.

December 2021: BioMed Alliance welcomes the adoption of the European Commission's proposal amending the IVDR transition periods

Ratio of IVD categories is highly diagnostic field-specific; on average only 52% are CE-IVDs used according to IFU



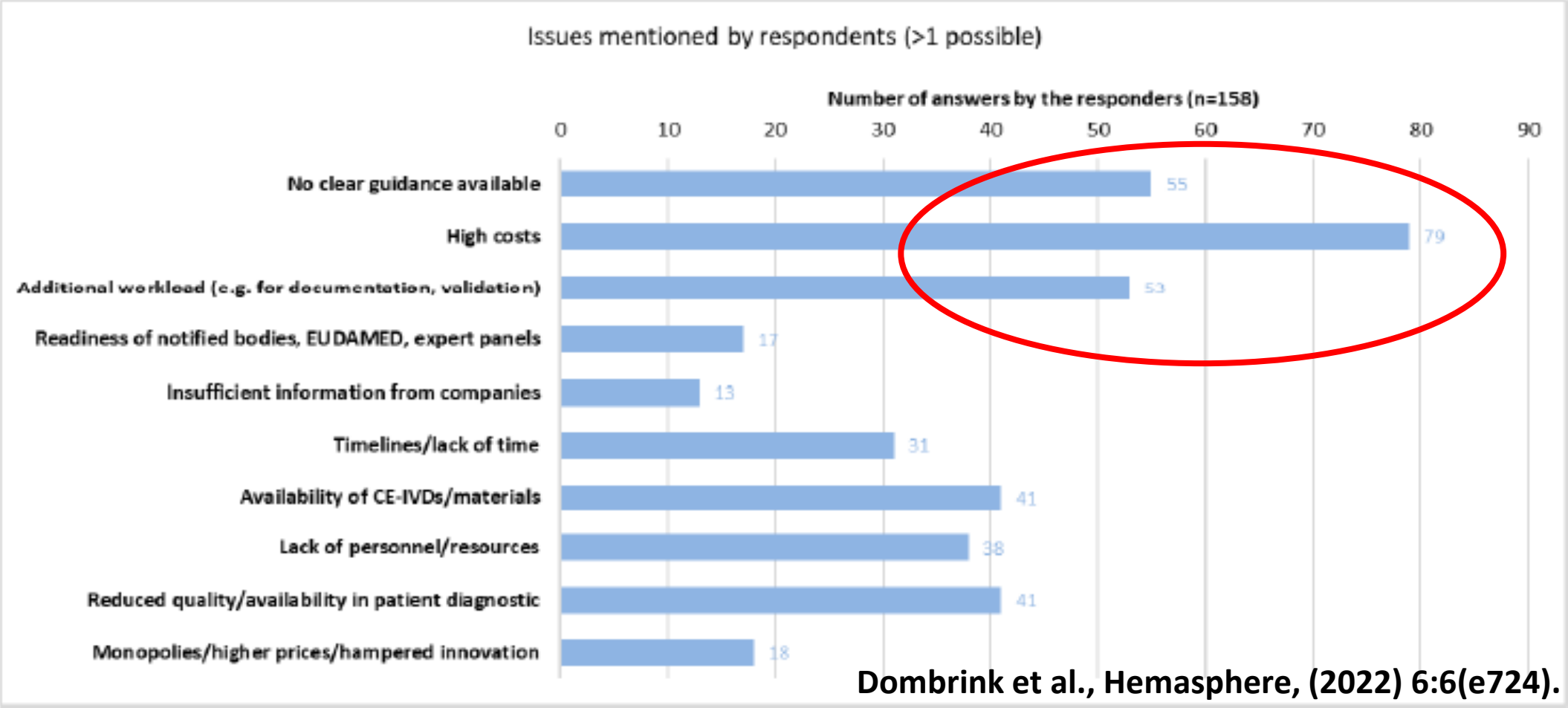
- **n=150 laboratories**
- **30,000** (overlapping) IVDs

Average % of tests from 5 categories:

- **52%** CE-IVDs
- **11%** CE-IVDs with minor modifications
- **3%** off-label CE-IVDs
- **8%** RUOs
- **26%** IH-IVDs

Dombrink et al., Hemasphere, (2022) 6:6(e724).

Issues mentioned by respondents in EU survey on IVDR roll out



Dombrink et al., Hemasphere, (2022) 6:6(e724).

reported more than one issue.

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Surveys demonstrate EU Regulatory System unpreparedness!

- Essential CE-marked tests may **disappear** from the European market.
- Specialty CE-marked tests, including companion diagnostics, will be particularly **vulnerable.**
- LDTs that currently complement CE-marked tests will be **embargoed** if there is any equivalent CE-marked alternative on the market, threatening access to innovative and specialized diagnostics.
- Personalised diagnostics and rare tests will not be developed and **monopolies** from unique CE-marked tests will limit diagnostic range.
- Creative solutions for rare diseases and health crises will be **hampered.**
- Serious concerns that the IVDR will **impede** the development of novel, specialized diagnostics and tests for rare diseases.
- Increase in **costs** of diagnostics.

- **Global increase in costs and bureaucracy and limitation to innovative diagnostics for questionable patient benefit!**

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VI. IVDR amendment & transitional provisions

In January 2022, Regulation (EU) 2022/112 was published, amending the EU IVDR's transitional provisions

Gives 3-5 more years for *most* tests CE marked under the former IVD Directive to transition to the IVDR

Keeps 26 May 2022 deadline for instruments and other lowest-risk IVDs

Overall, the amendment should for now **save *existing* CE marked tests…but not *innovations***

Gives 2-6 years transition for most IVDR requirements for lab-developed tests

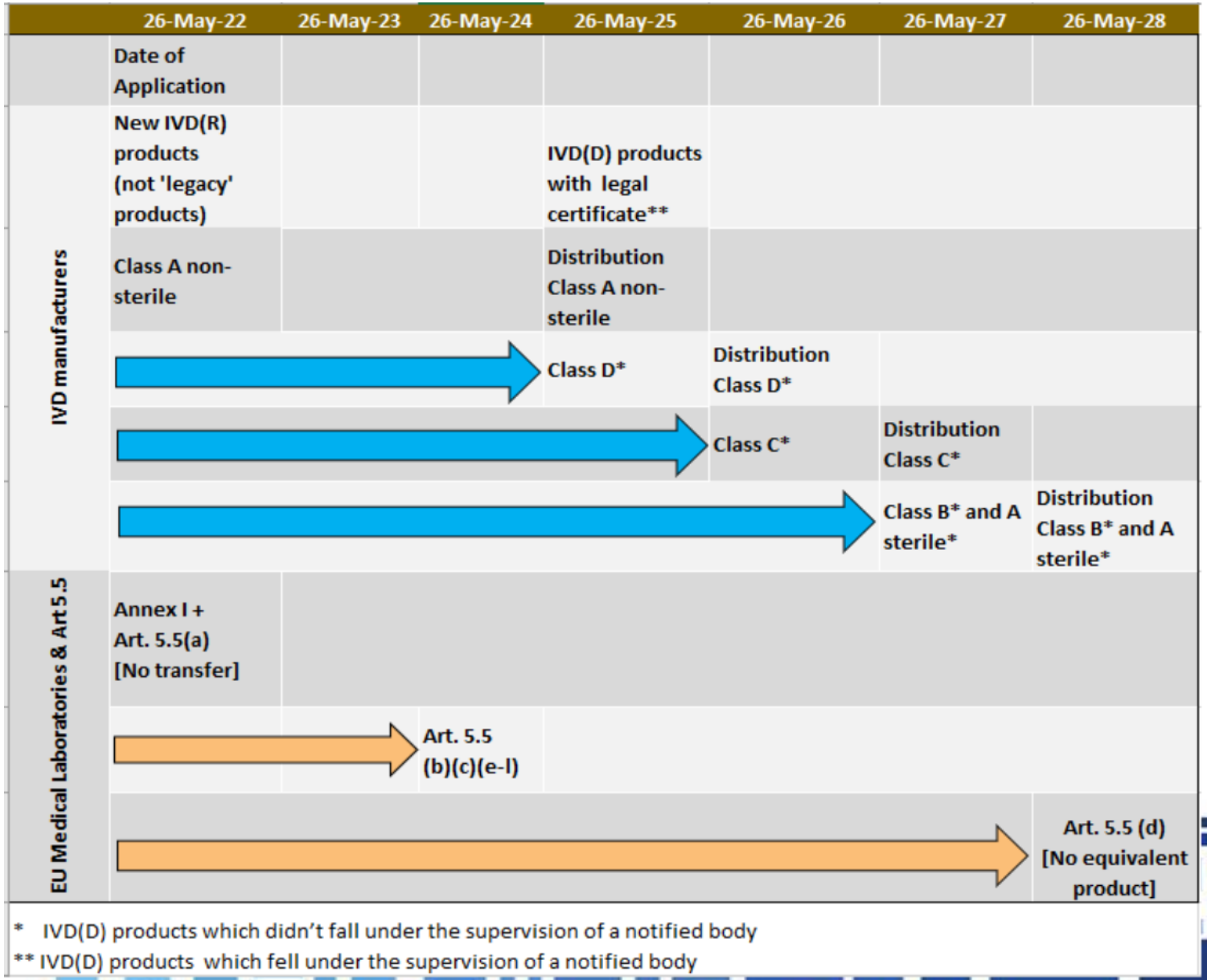
Regulation (EU) 2022/112 gives 3-5 more years for 'legacy' CE marked tests to transition in full to the EU IVDR…

CE-IVDs

Compliance to IVDR to be documented by IVD-industry

IH-IVDs

Compliance to Annex I and Art 5.5. to be documented by accredited labs



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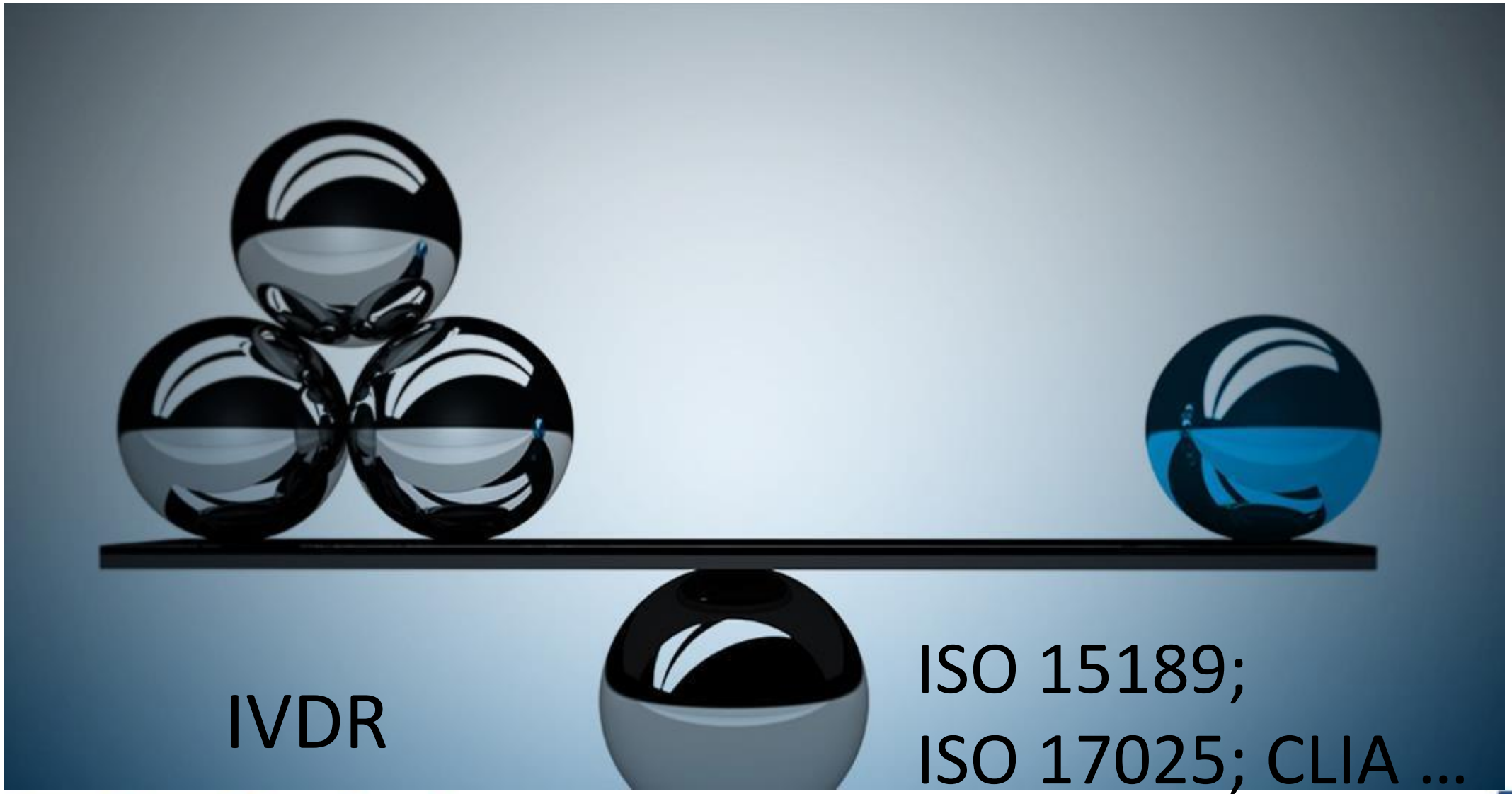
VII. How to maintain innovative LDTs?



Relation between the ISO 15189 standard and the IVDR

Given the **IMPORTANT OVERLAP BETWEEN ISO 15189 AND THE IVDR**, in particular regarding equipment, reagents and other *in vitro* diagnostic medical devices, **ISO 15189 is an important basis for compliance to the IVDR** for diagnostic laboratories. At the same time, ISO 15189 covers a much broader range of quality and safety of diagnostics, risk management, personnel, and reporting.

REGULATORY STRATEGY FOR LDTs in compliance with international State-of-the-Art Regulations and the EU IVDR

Key elements for LDT Regulation in EU

1. QMS
2. Risk-based approach for LDT classification
3. Risk management system
4. Evaluation and documentation of LDTs related to essential requirements for quality, safety and performance
5. Product monitoring and surveillance
6. Justification for use
7. Regulatory oversight mechanism

And more collaborative efforts (ERNs) & concerted actions between stakeholders!

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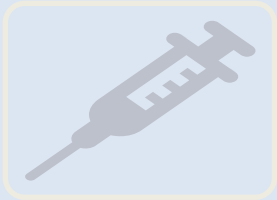
VIII. Conclusions



The EU Regulatory Infrastructure is still under construction. Bottle necks for test market access are the limited number of Notified Bodies and common specifications, among others.

IVDR compliance is a major effort for IVD-manufacturers and diagnostic laboratories, requiring evidence for safety, performance and quality.

Prolongation of the transition timelines prevented a diagnostic collapse per date-of-application but capacity problems at the level of Notified Bodies have not been solved yet!

Developing an EU-wide Regulatory Strategy for LDTs, in compliance with international state-of-the-art and IVD Regulation, is key to maintain and extend innovative diagnostics at a reasonable cost.

Thanks for your attention