



EUROPEAN FEDERATION OF CLINICAL CHEMISTRY
AND LABORATORY MEDICINE

The New EU IVD Regulation 2017/746: What to expect and how to prepare your Laboratory?

Prof. Dr. C.M. Cobbaert

Laboratory Specialist in Clinical Chemistry & Lab Medicine

Chair EFLM Task Force on European Regulatory Affairs

EC observer to MDCG IVD group

ECAT symposium, 15-16 September 2022



www.eflm.eu

Content

I. Rationale

II. IVDR key changes

III. Transitioning from IVDD to IVDR: original timelines & consequences

IV. Forecast on CE-IVD availability < market survey in July 2021

V. Lab preparedness for LDTs < survey report December 2021

VI. Amended IVDR timelines

VII. How to maintain innovative LDTs under the IVDR?

VIII. Conclusions

I. Rationale for the IVD Regulation

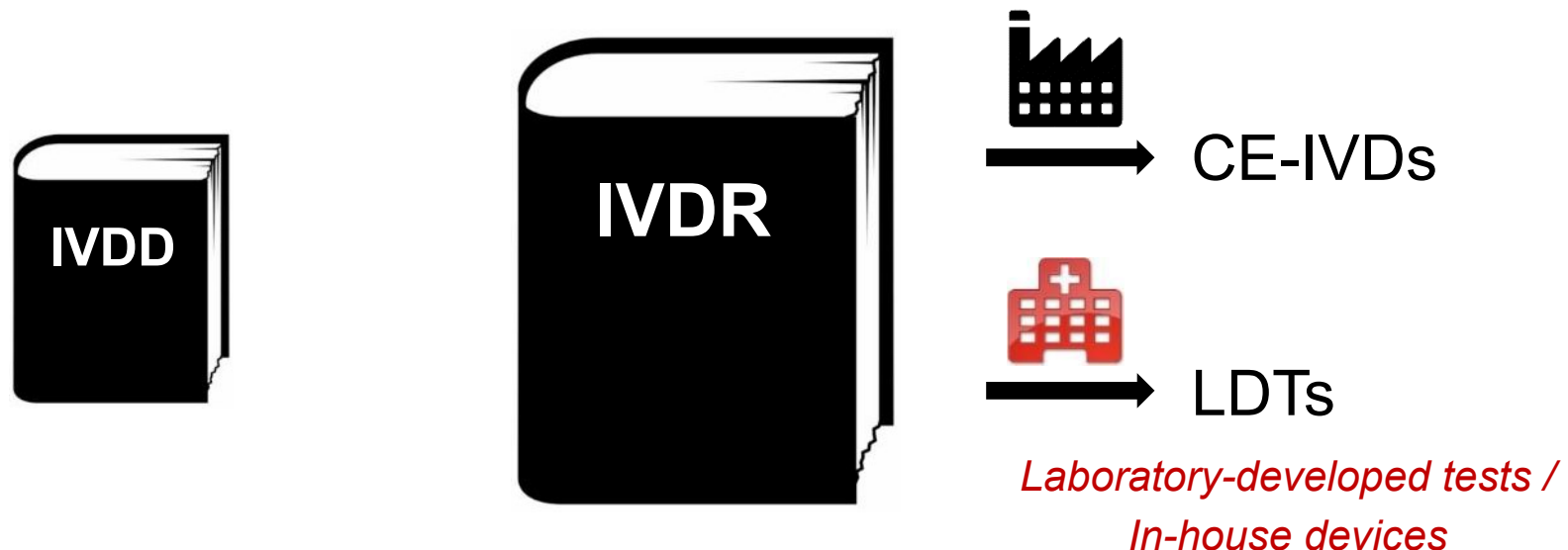


The purpose of IVDR legislation is to **regulate the trade in IVDs in the EU** and, and by doing so, to guarantee the **safety, suitability and performance** as well as safeguard the **health** and ensure the necessary **protection** of patients, users and other persons.



Since 26 May 2022: from IVDD to IVDR

- IVDD regulates commercial IVDs (CE-IVDs)
- IVDR regulates CE-IVDs and In House-IVDs (LDTs)



1998 - 2022

Entry into force: 2017

5 years for Implementation

Date of application: May 26th, 2022

ECAT symposium, 15-09-22

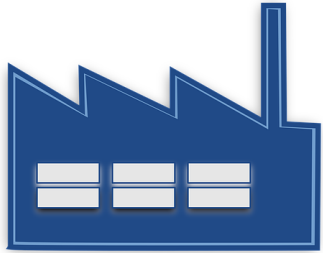
Structure of the IVDR and recommended reading 1/2

IVDR part	Number	Title	Recommended reading <i>(Parts indicated in red apply to IH-IVDs)</i>
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

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)	-

Areas of the regulatory framework



Pre-market



Post-market



Qualification/
classification

Conformity
assessment

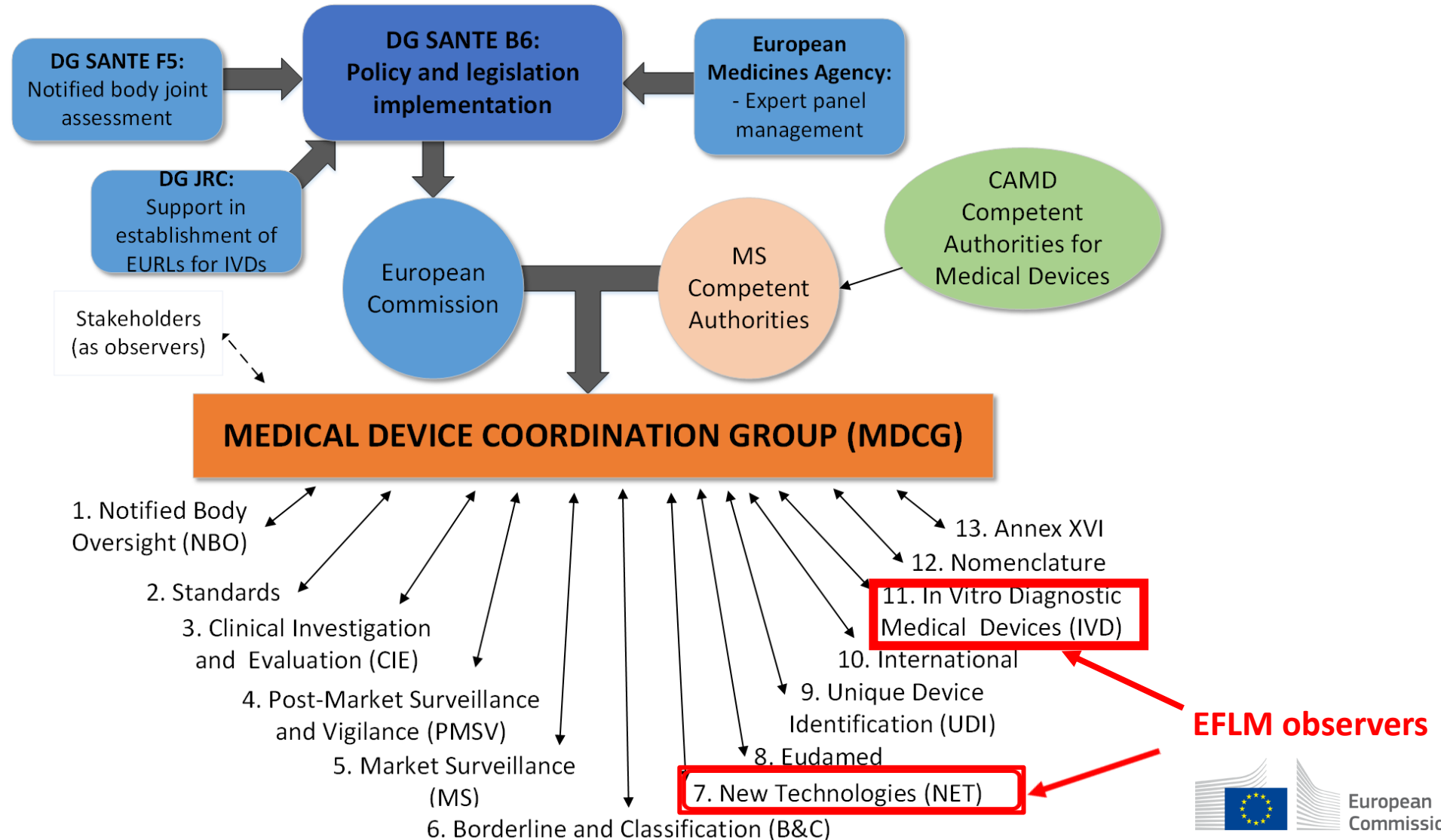
Performance
evaluation/
performance study

Post-market
surveillance
(manufacturer)

Market surveillance
(competent
authorities)

Vigilance

Governance of EU-level implementation work



II. IVDR key changes

1. Scope enlargement & (Re)Classification
2. Clinical Evidence Requirements
3. Notified bodies and Conformity Assessment
for ~ 85% of commercial tests (classes B, C, D);
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)

Opportunities

Threats!?



Readiness 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,).

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
fall under the IVDR, not pathology services!

Scope Enlargement

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

- (a) Concerning a physiological process of state;
- (b) Concerning congenital physical or mental characteristics;
- (c) Concerning the predisposition to a medical condition or disease;
- (d) To determine the safety and compatibility with potential recipients;
- (e) To predict treatment response or reactions;
- (f) To define or monitor therapeutic 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.

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

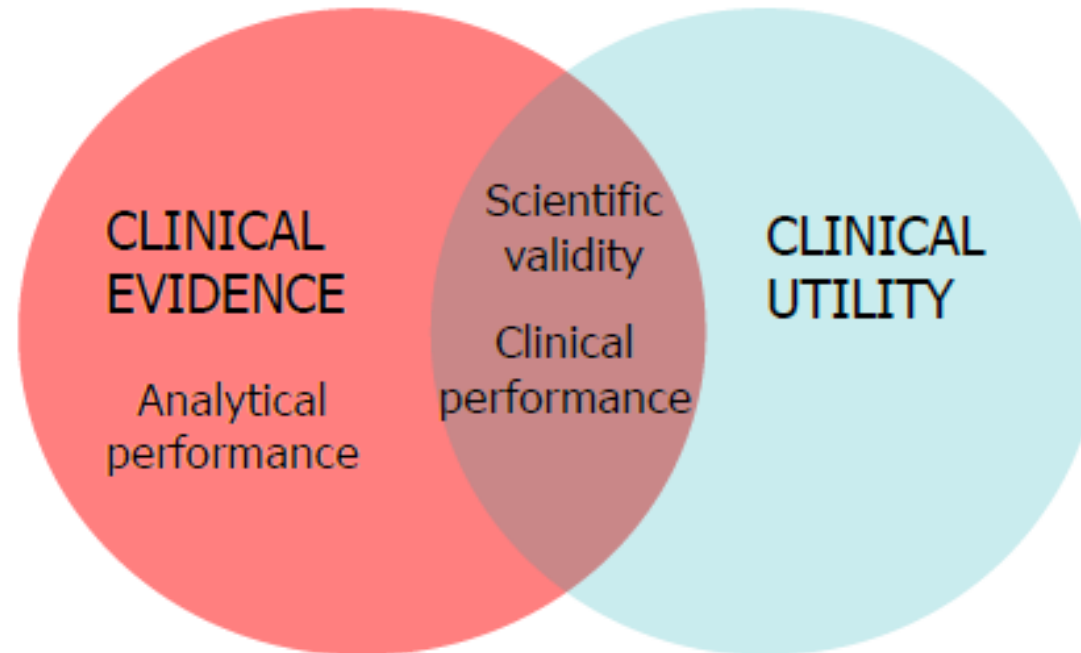
- Low risk for individual patients
- Instruments, accessories, specimen collection systems etc.

CCLM 2021, Cobbaert et al.

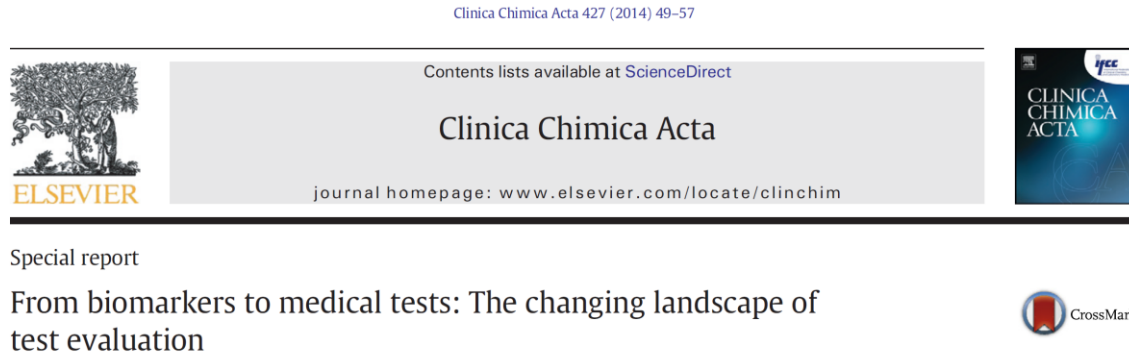
Clinical Evidence Requirements

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.**



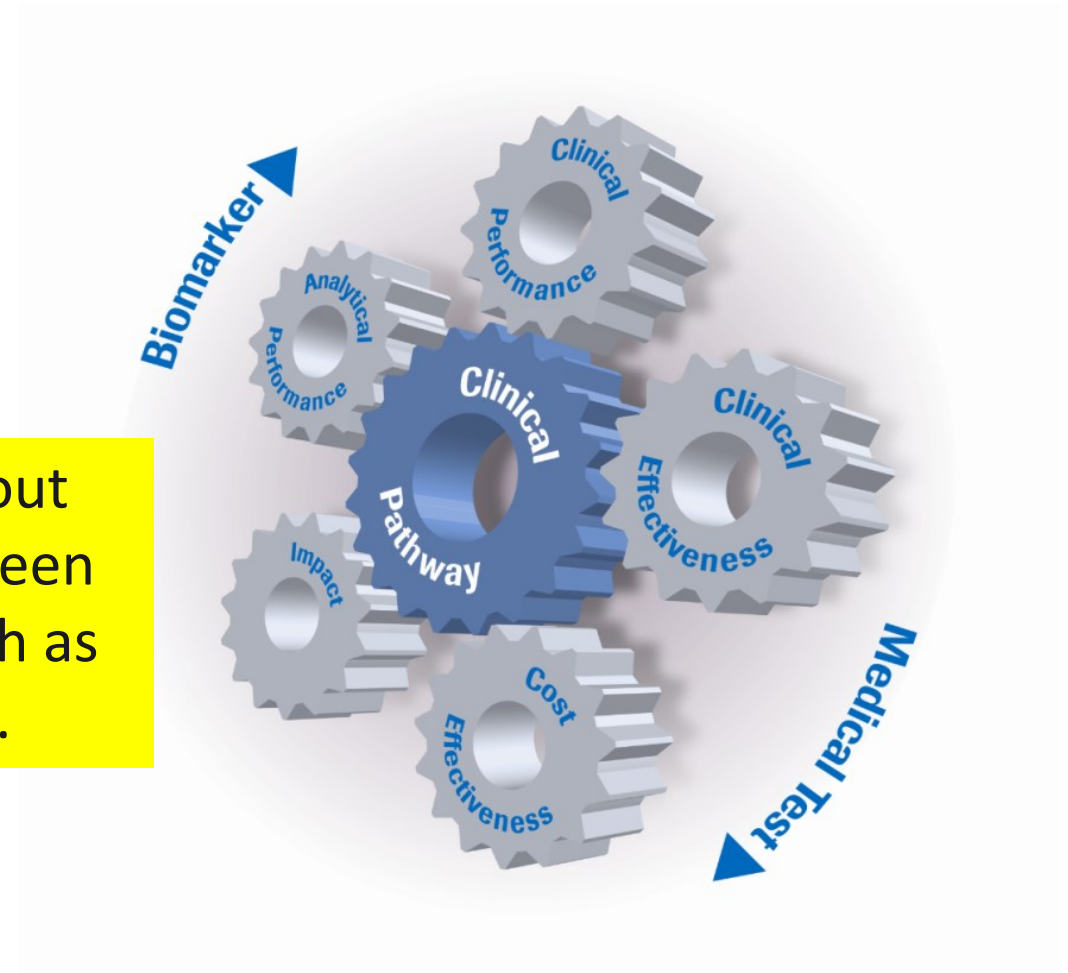
From biomarkers to medically useful tests



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.



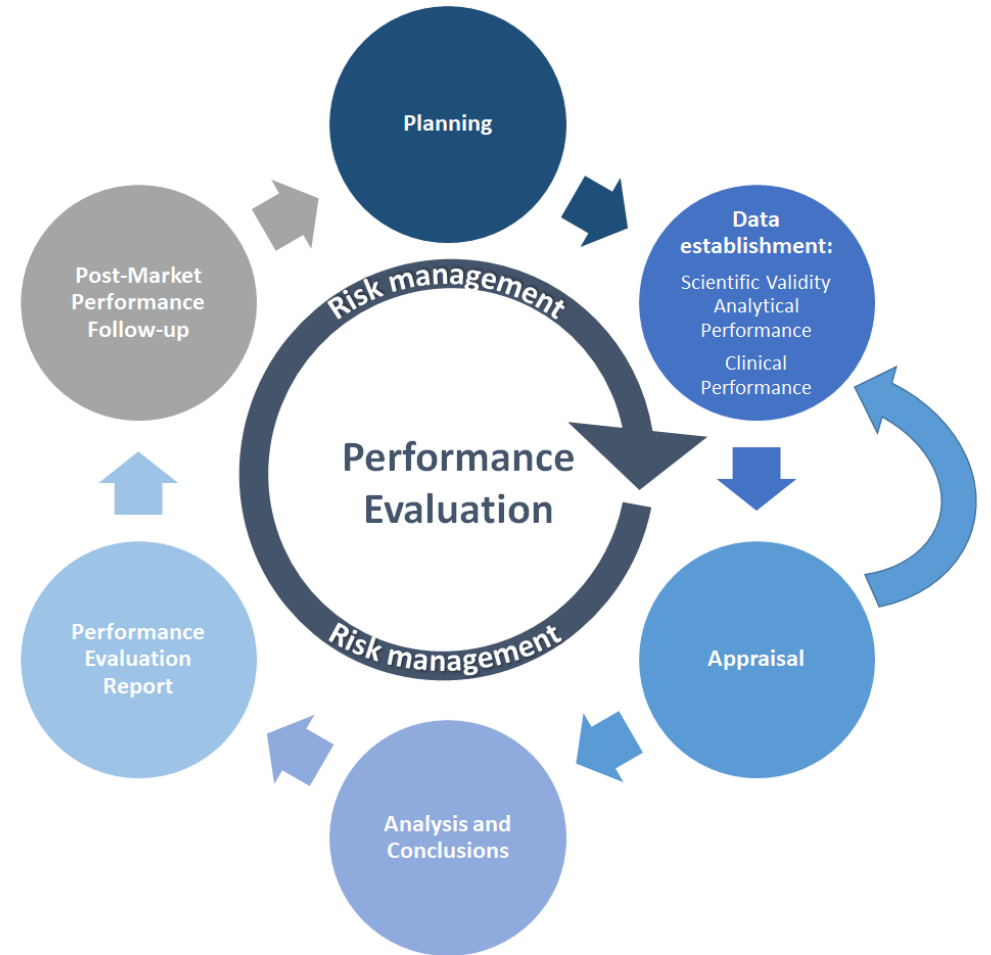
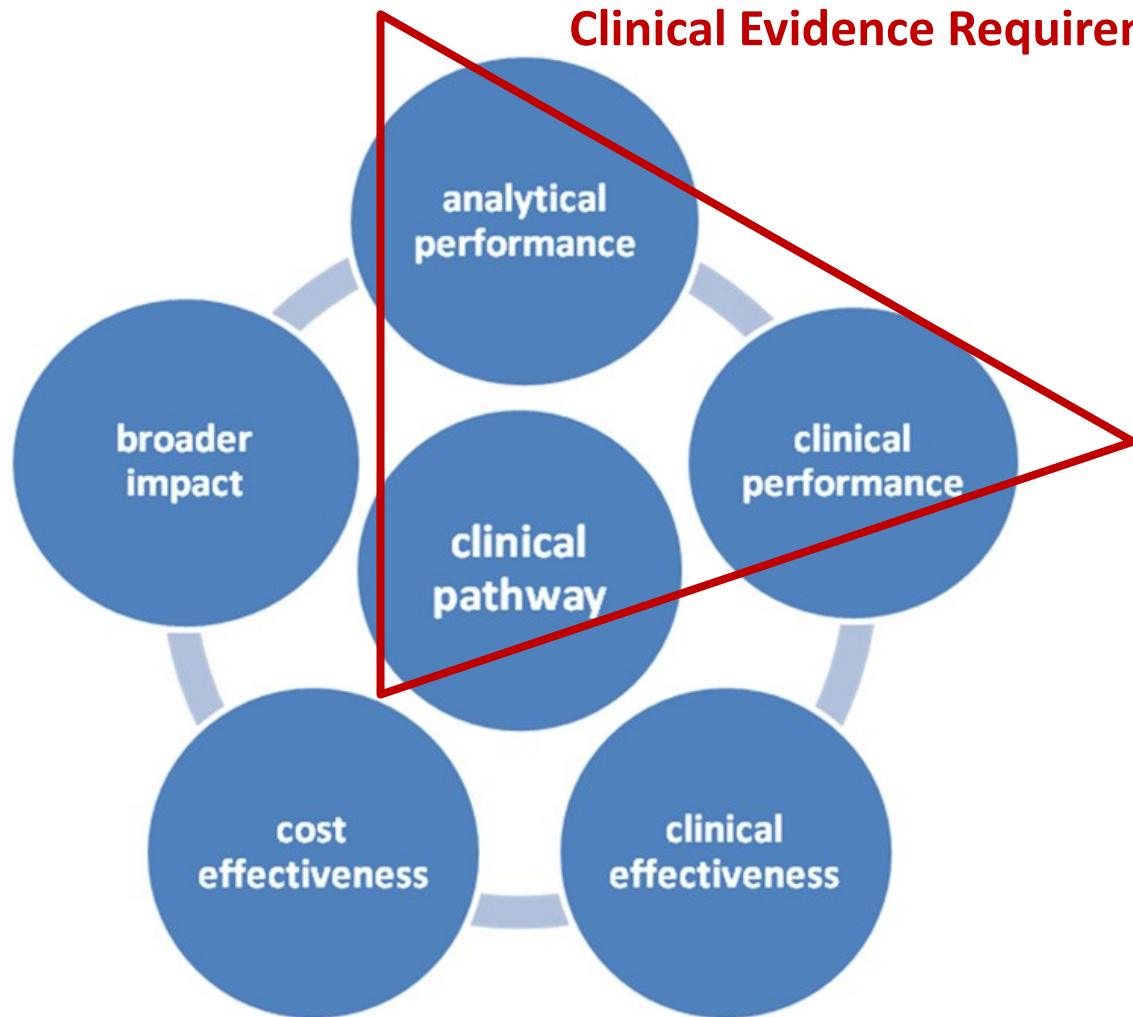
ECAT symposium, 15-09-22



Clin Chim Acta 2014;427:49-57

Clin Chim Acta 2016;460:211-219

IVDR 2071/746 superposed on EFLM Test Evaluation framework

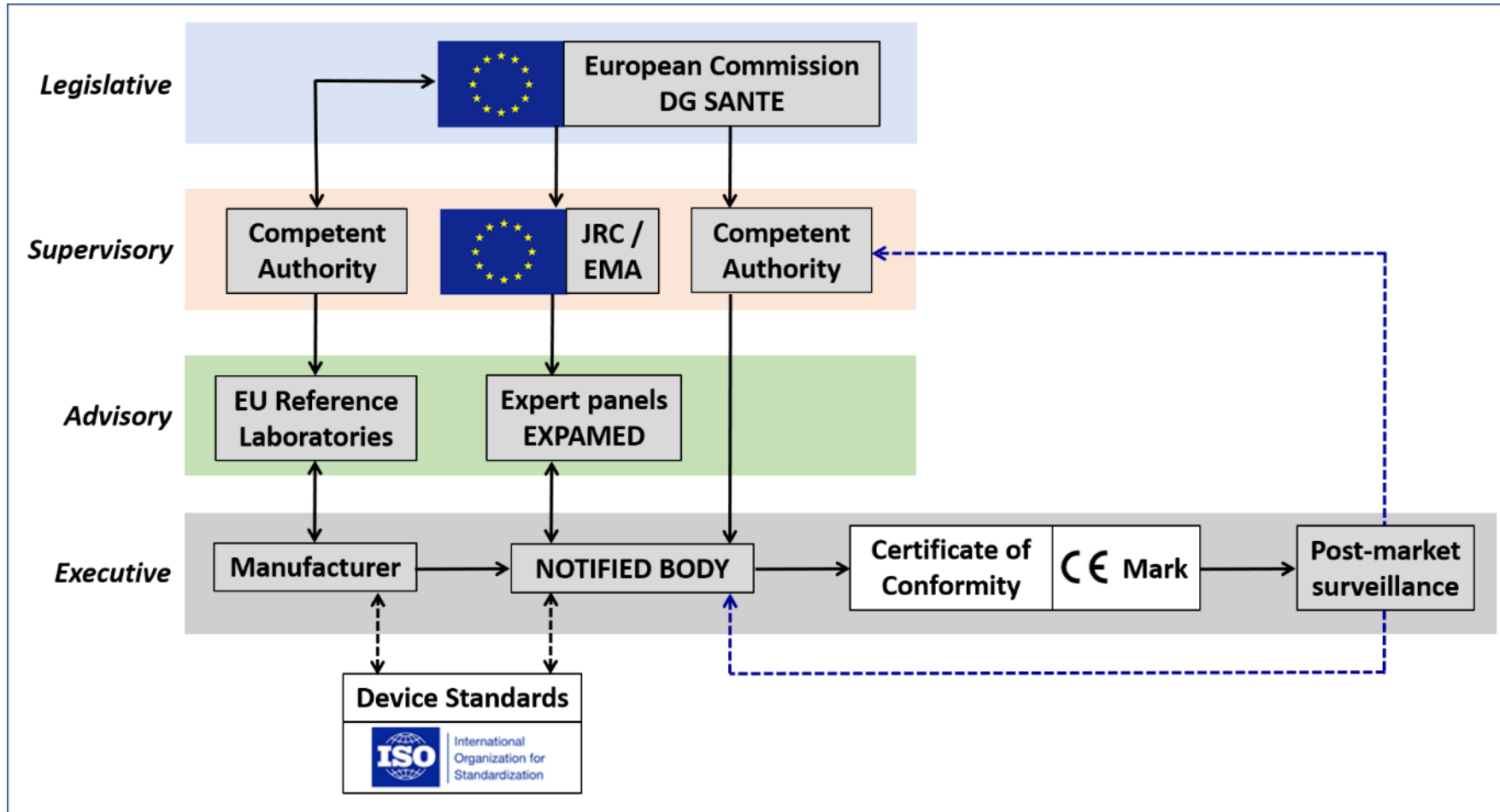


Medical tests should be fit-for-clinical-purpose THROUGH THEIR ENTIRE LIFE CYCLE (PEP and PMPF)!

Performance Evaluation Plan (PEP) – Recital (61)

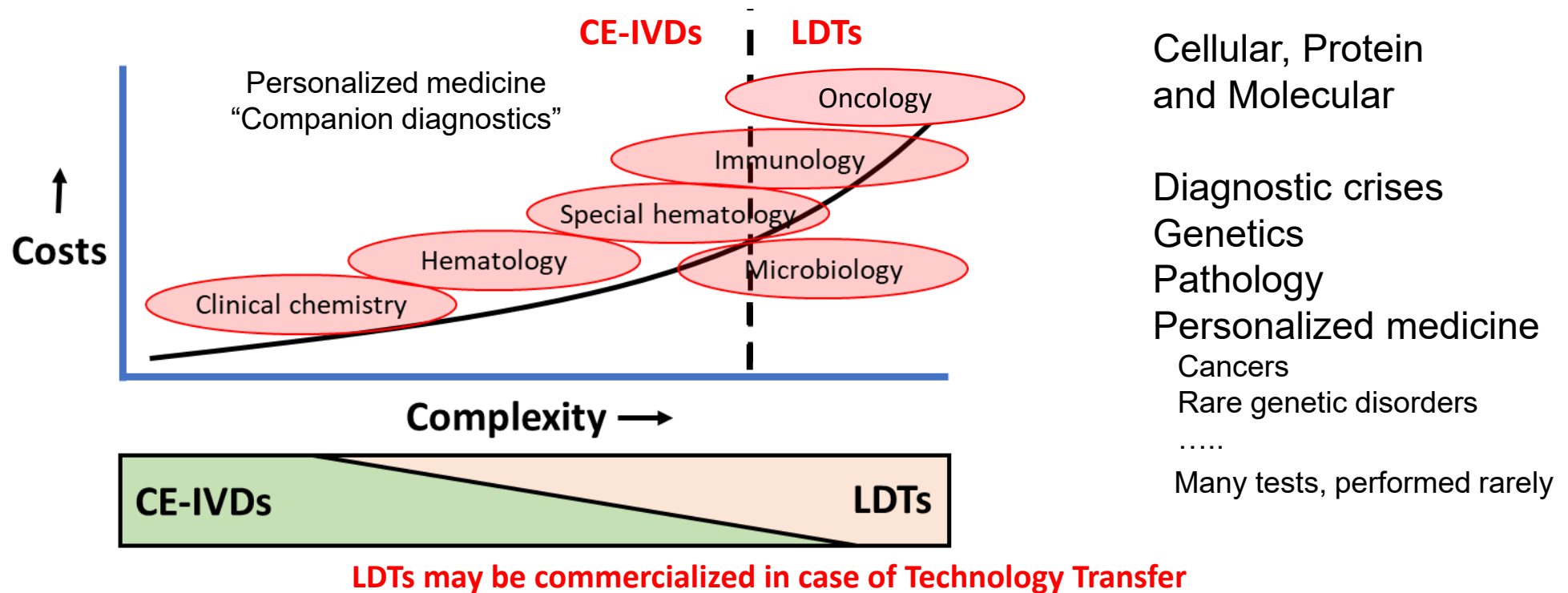
Post-market Performance Follow-up (PMPF) – Recital (63)

Third Party Review for 85% of medical tests: Conformity Assessment Process of CE-IVDs under the IVDR



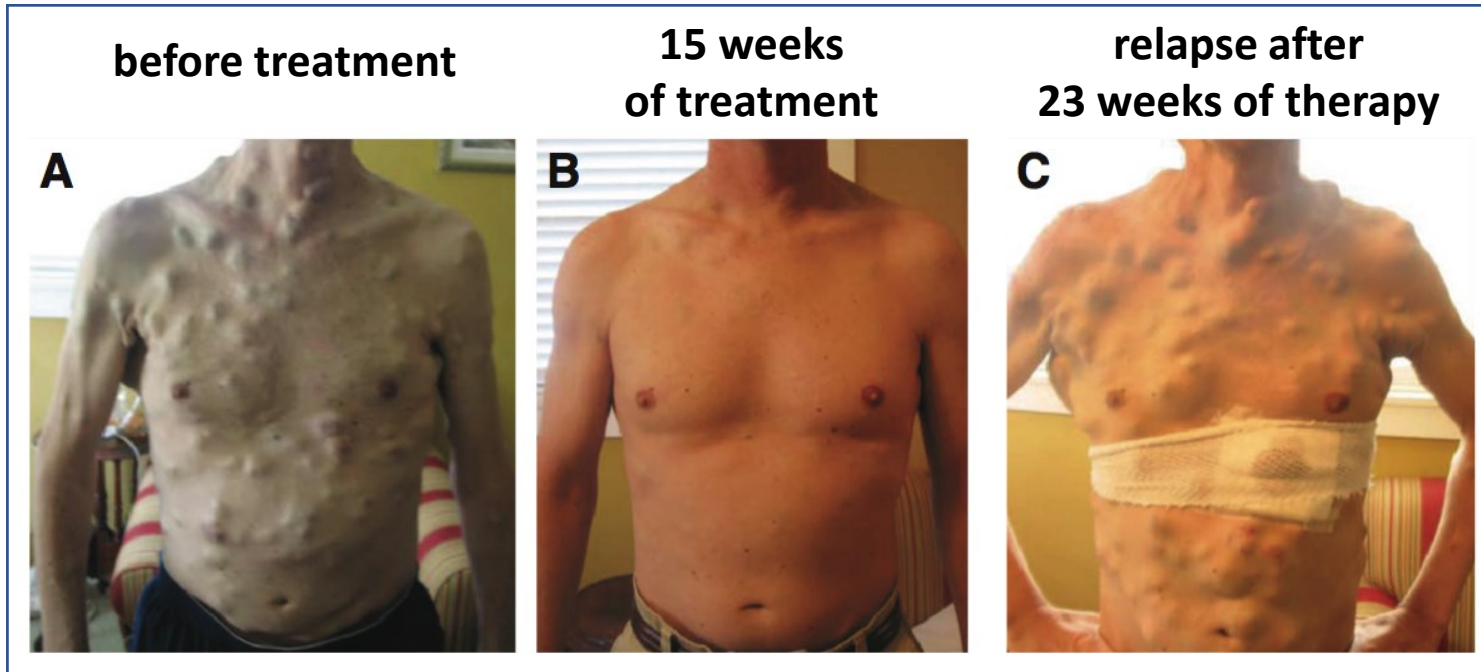
Cobbaert et al., CCLM 2022; 60(1): 33-43.

Running high complexity in-house tests comes with obligations

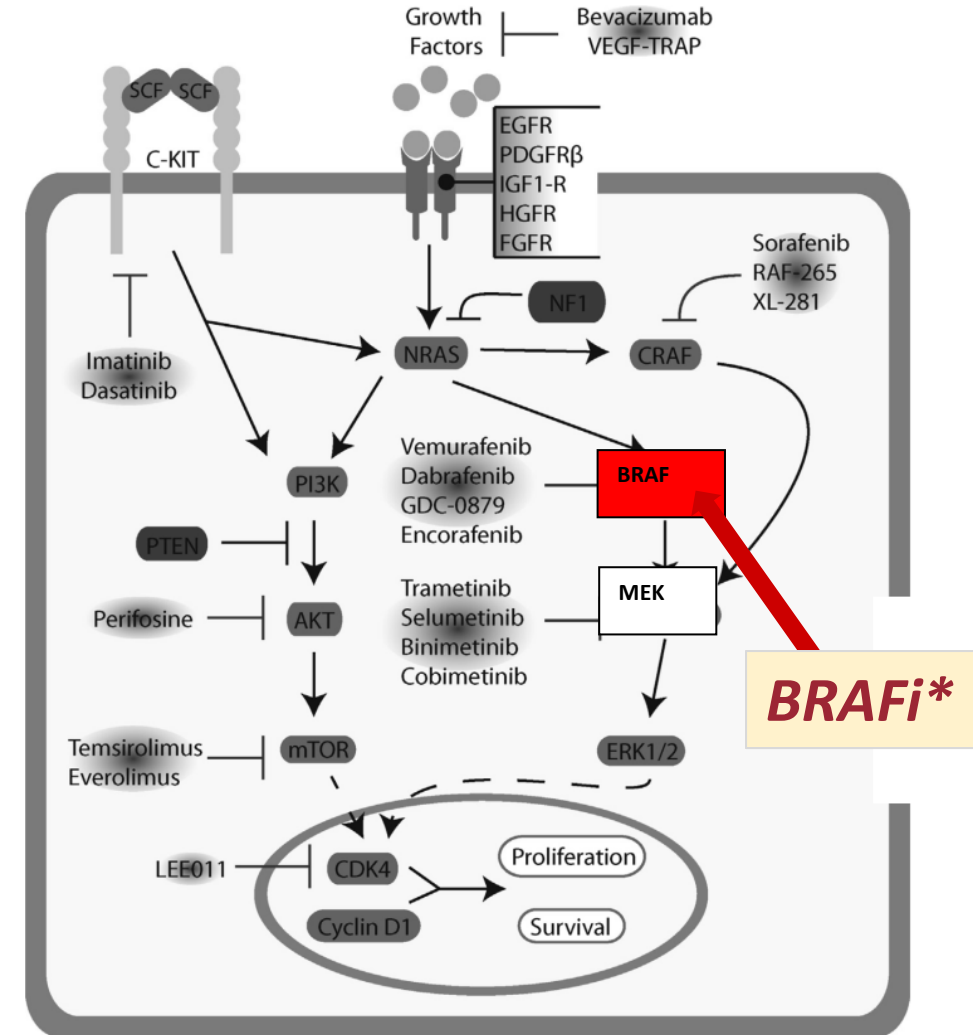


- Assays with higher complexity are more difficult to commercialize
- To provide optimal healthcare, diagnostic laboratories depend on development of LDTs for many (complex) applications
- This dependence differs significantly per diagnostic field

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)

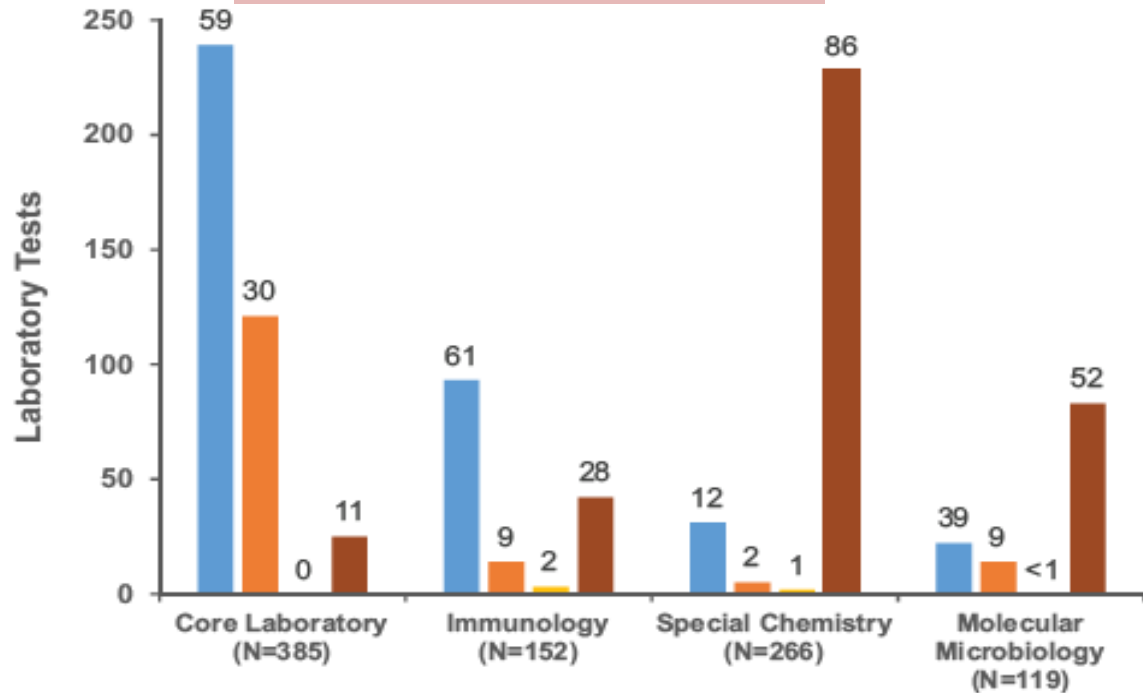


* *BRAFi* inhibitor therapy

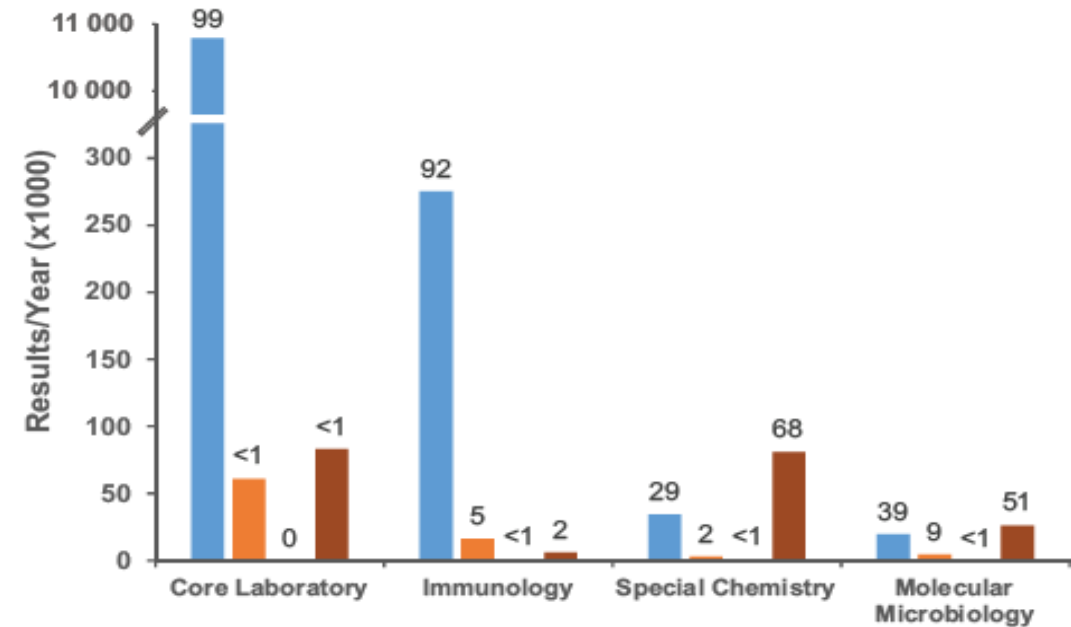
By courtesy of Prof M. Neumaier

LDTs play a vital role in diagnostics

**42% of all tests
CE-IVDs**



**98% of all results
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.

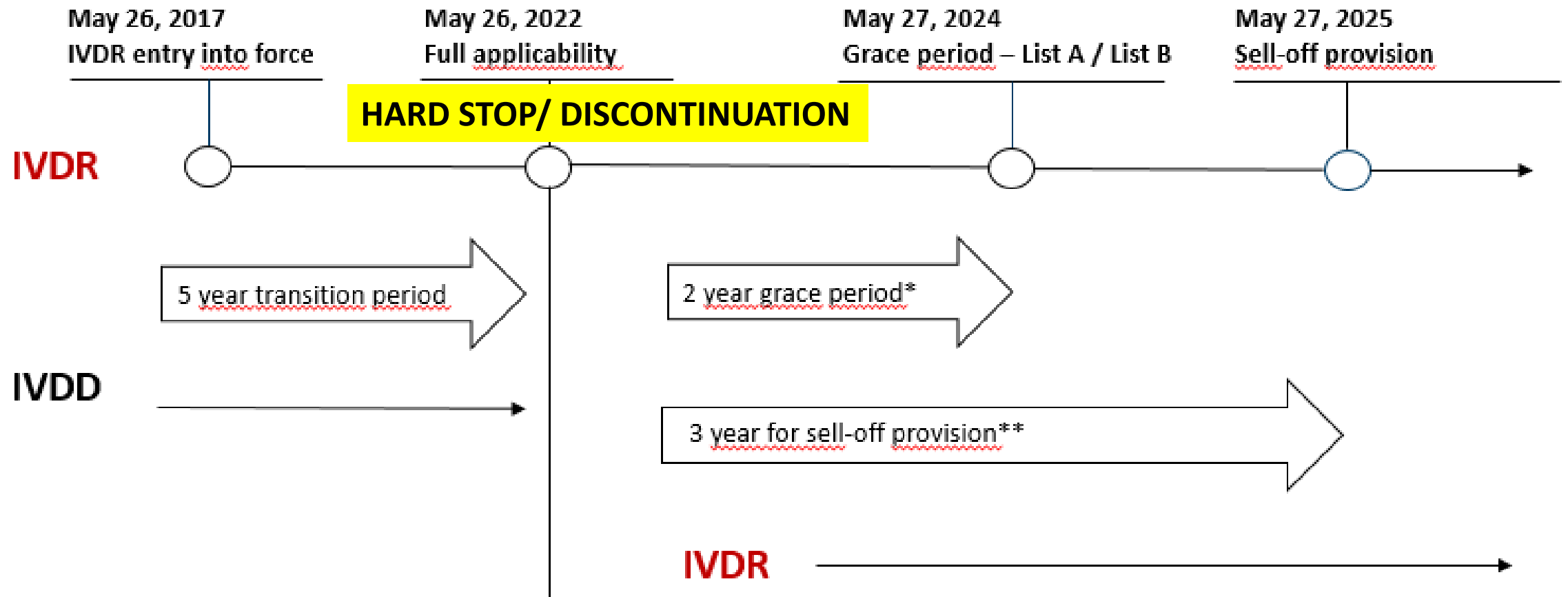
Vermeersch P et al., Clin Chem Lab Med 2020

Conditions 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 this Regulation **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;

III. Original IVDR implementation timelines



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

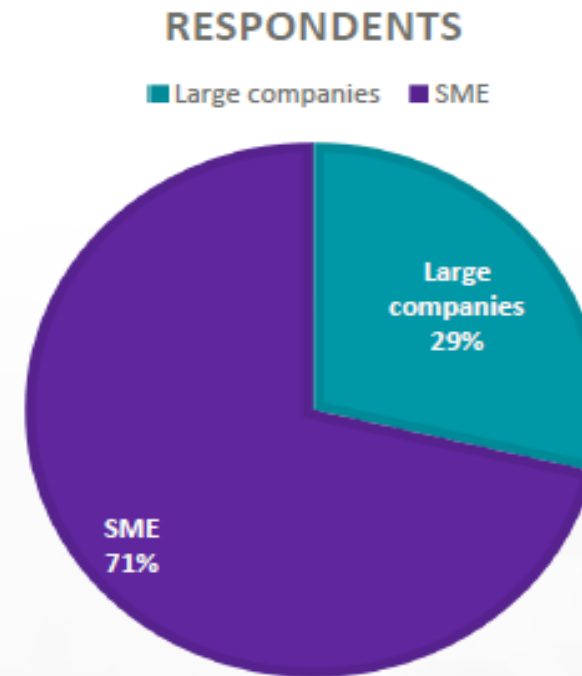
** IVDD devices which have been put in the supplier warehouses before May 26, 2022 and have not reached their final user can be sold until May 27, 2025 latest or until the expiry date is reached.

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

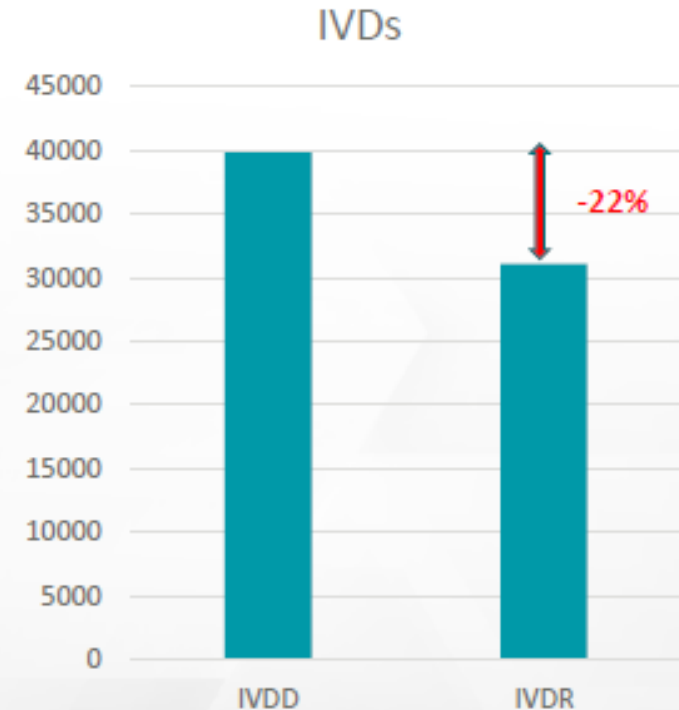
IVDs on the market under IVDD and IVDR

	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

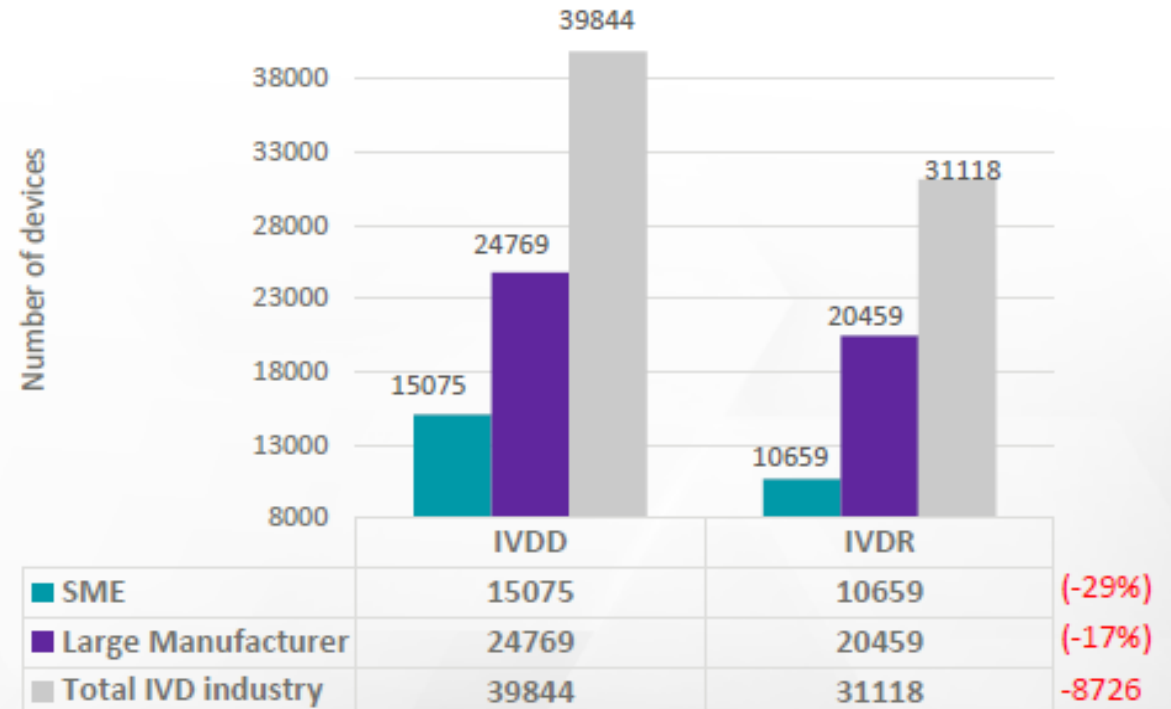


Market Survey in July 2021

Number of IVD's on the market under IVDD and IVDR by company size

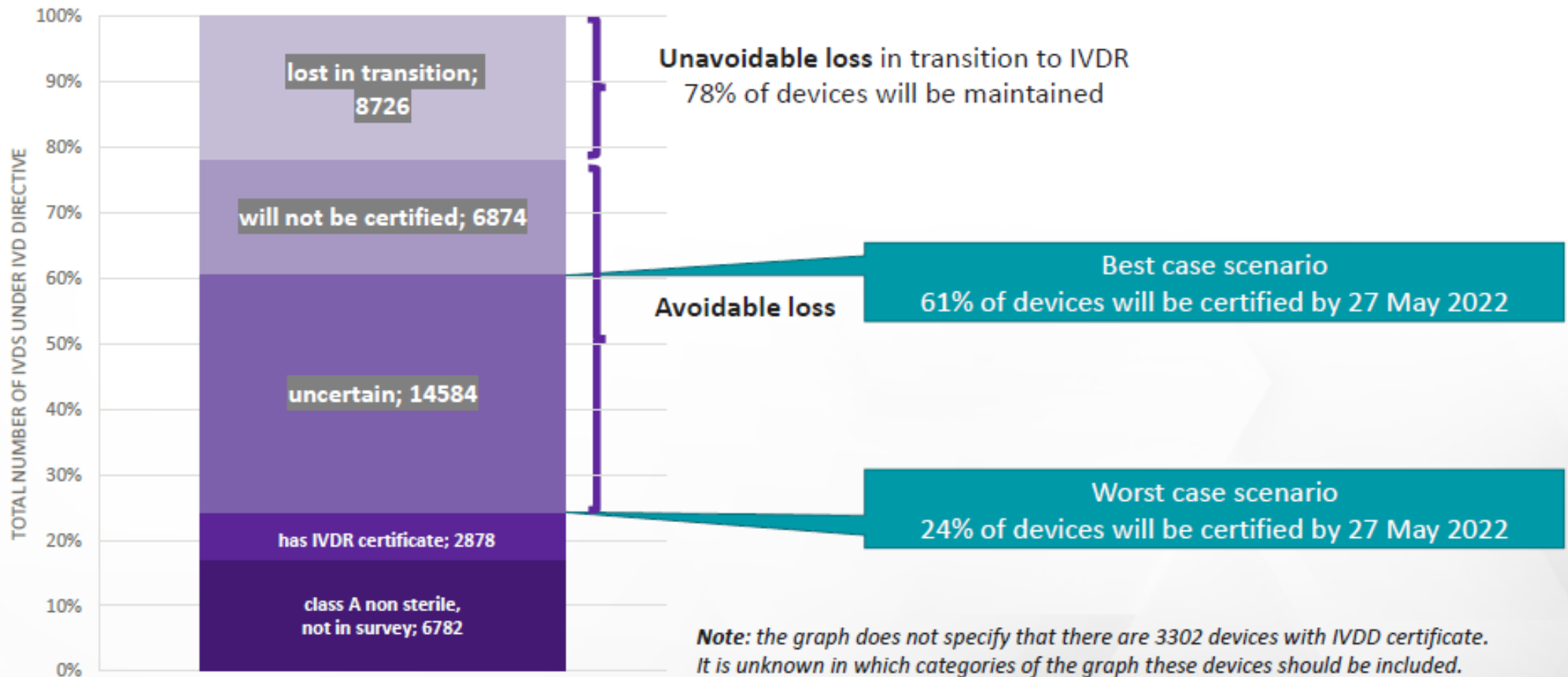
SME manufacturers expect to lose the greatest share (29%) of their products when considering which IVDs they will keep from IVDD to IVDR

Total number of IVD devices under IVDD and IVDR



Forecast based on Market Survey in July 2021

Forecast: % of IVDs expected to be certified under IVDR by 27 May 2022



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

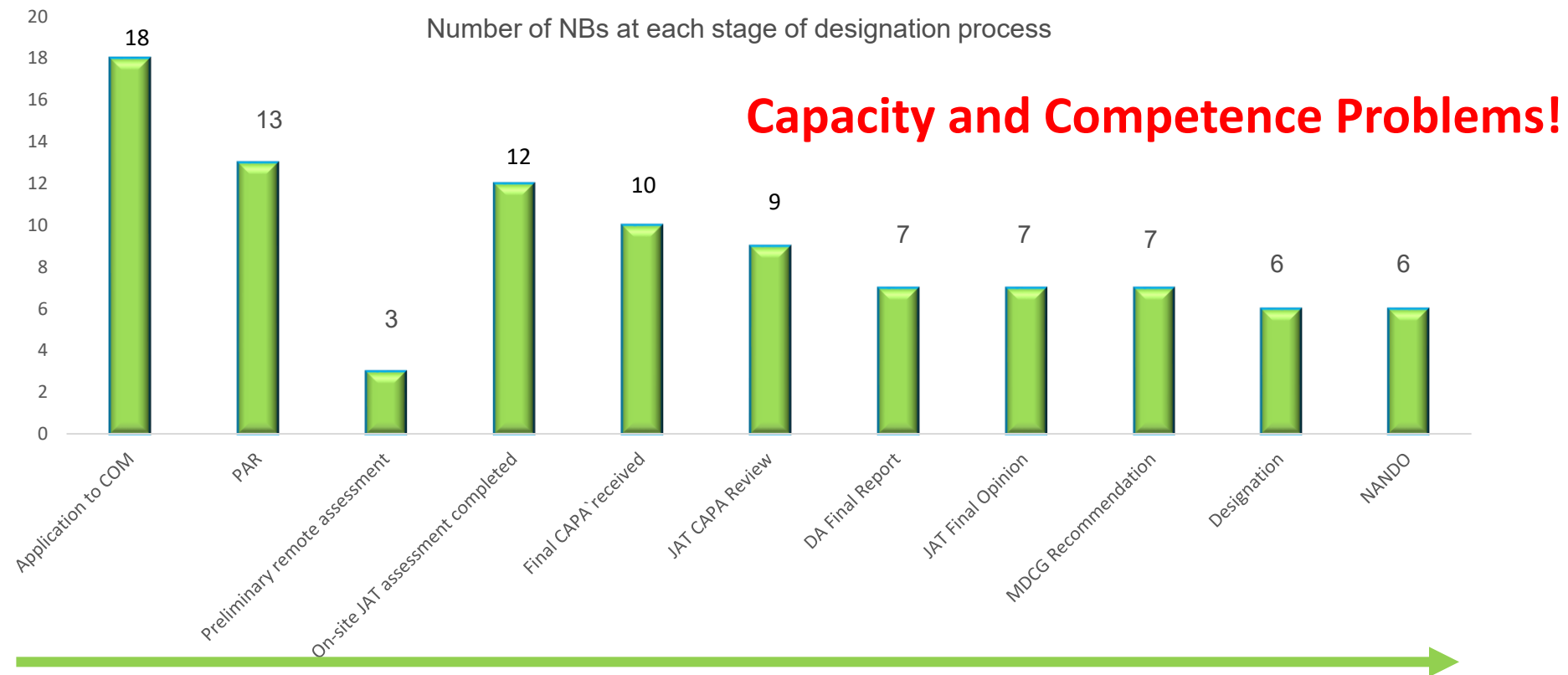
Implementation of the new EU IVD regulation – urgent initiatives are needed to avert impending crisis

Status of EU-level IVDR infrastructure, April 2022

Element	Legal requirement for device market access?	Ready?
Notified bodies	YES	YES but only 7 so far
EMA companion diagnostic consultation	YES	YES
Expert panel (class D)	YES	YES
Unique device identification system	YES	YES
Nomenclature	YES	YES
Eudamed database	NO	In preparation
EU reference laboratories (class D)	NO	In preparation (for 2023)
Common specifications	NO	In preparation (1 st batch 2022)
Harmonised standards*	NO	YES some
Guidance documents	NO	YES some

Notified bodies

- 7 NBs designated so far: [NANDO database](#)
- Average length of designation process ~2.5 years
- Timing mostly depends on candidate NB & national designating authority





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

HemaSphere



HemaPolicy
Open Access

Critical Implications of IVDR for Innovation in Diagnostics: Input From the BioMed Alliance Diagnostics Task Force

Main Findings IVDR Questionnaire BioMed Alliance. 2021.

Available at: <https://www.biomedeuropa.org/images/news/2021/20211206>.

[Findings IVDR Questionnaire final.pdf](#).

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



Biomedical Alliance in Europe

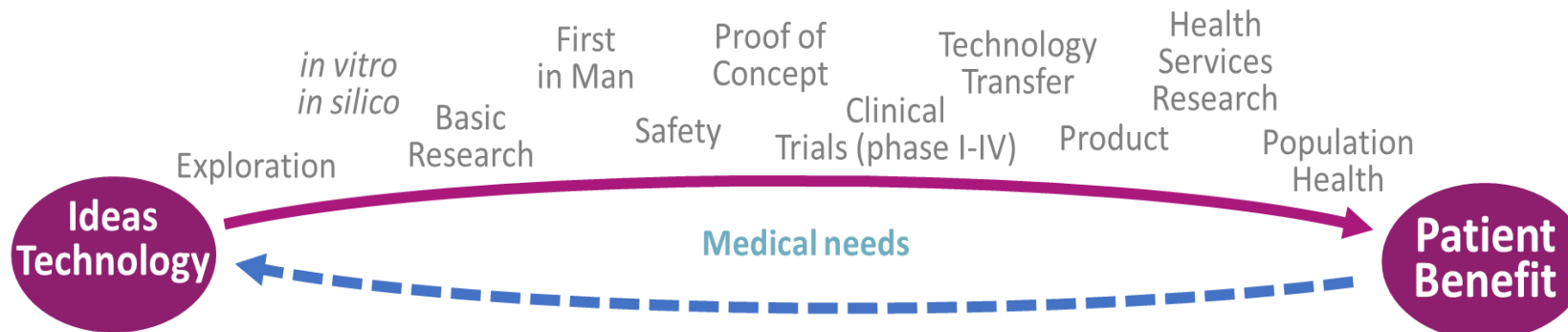
**September 2021 Meeting with the European Commission
to find a way out to prevent a diagnostic collapse**

Mission BMA



Improve the health and wellbeing of citizens in Europe

- a **unique initiative** of 36 European medical societies that together include more than 400,000 researchers and health professionals
- Speaks as a **common voice** for all its members
- Represents the **translational value chain** from basic research to clinical treatment
- Promotes excellence in European biomedical research and translation for the **benefit of patients**





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

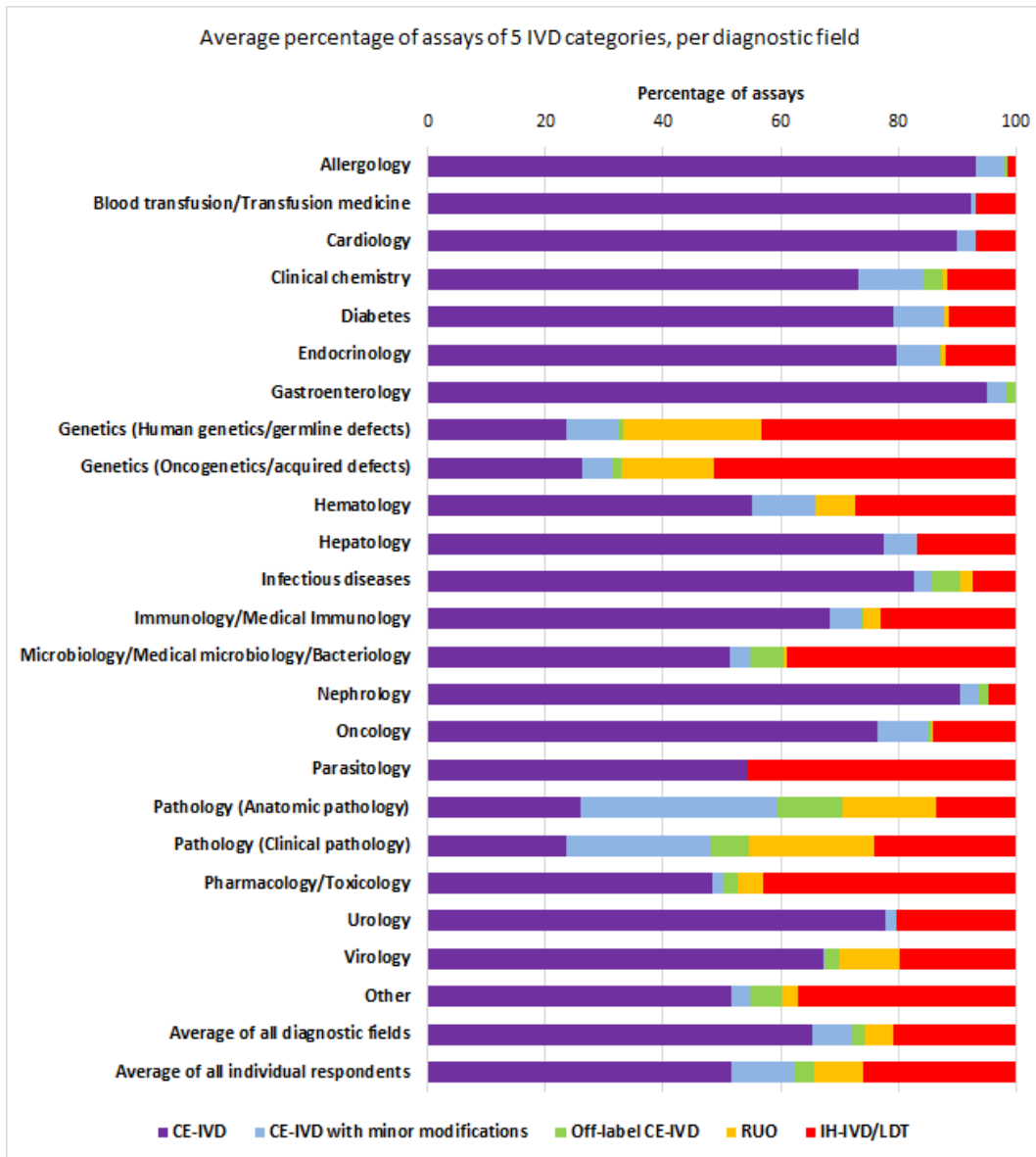
October 2021: Welcoming the amending act and extended transitional provisions. As a result of the BioMed Alliance and EFLM advocacy efforts, extended provisions are provided for in-house devices as well (Art. 5.5).

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

Issues mentioned by respondents in EU survey on IVDR roll out

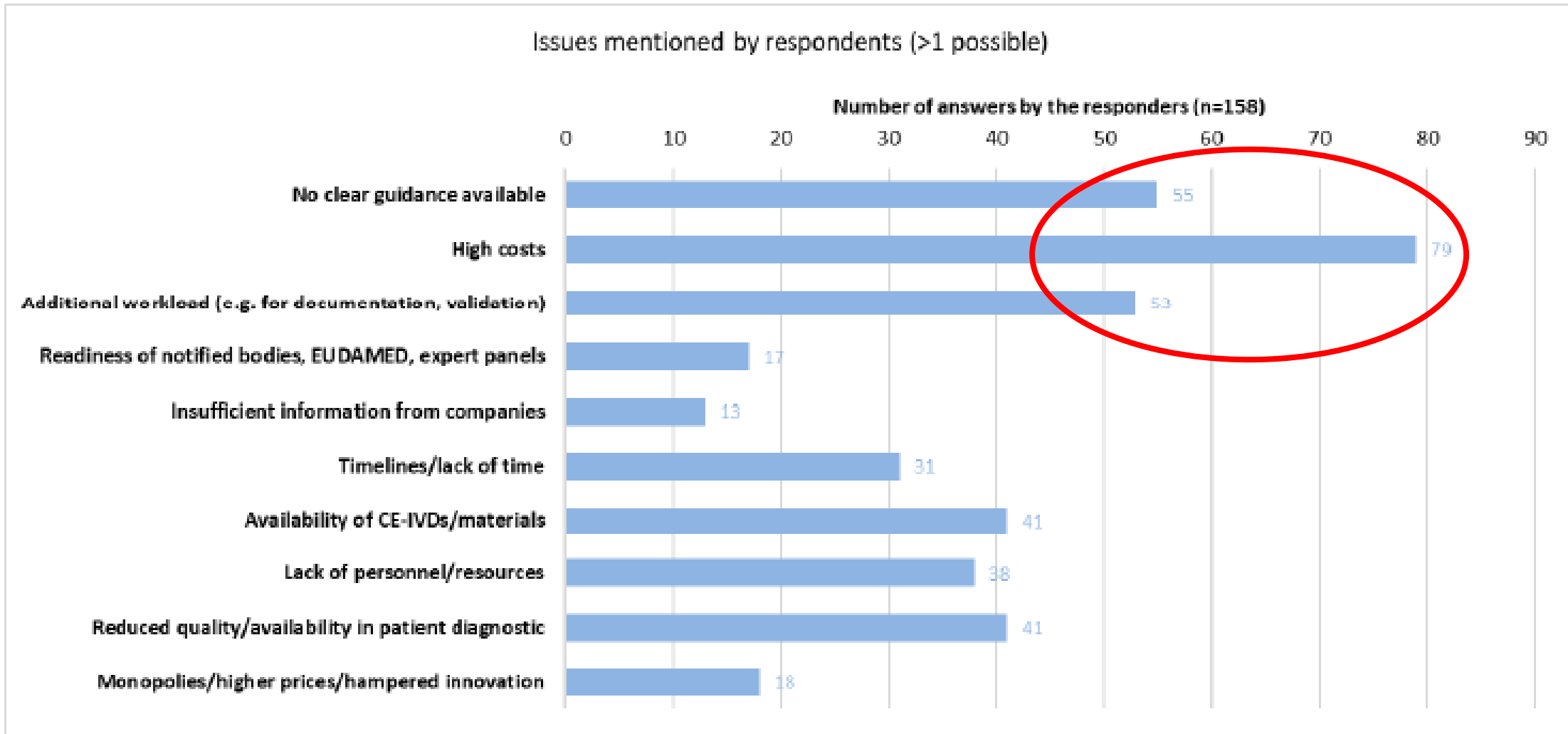


Figure 13. Issues that respondents (n=158) are/expect to be facing during their preparations for the IVDR. Some respondents reported more than one issue.

Impact of the IVDR roll out & 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**

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

		26-May-22	26-May-23	26-May-24	26-May-25	26-May-26	26-May-27	26-May-28
	Date of Application							
IVD manufacturers	New IVD(R) products (not 'legacy' products)				IVD(D) products with legal certificate**			
	Class A non-sterile				Distribution Class A non-sterile			
					Class D*	Distribution Class D*		
						Class C*	Distribution Class C*	
						Class B* and A sterile*	Distribution Class B* and A sterile*	
EU Medical Laboratories & Art 5.5	Annex I + Art. 5.5(a) [No transfer]							
				Art. 5.5 (b)(c)(e-l)				
								Art. 5.5 (d) [No equivalent product]

* IVD(D) products which didn't fall under the supervision of a notified body

** IVD(D) products which fell under the supervision of a notified body

VII. How to maintain innovative LDTs under the IVDR?



Relation between the ISO 15189 standard and the IVDR

ISO 15189: Quality and competence for medical laboratories

(e.g. management, personnel, accommodation, equipment, reagents, (pre/post) examination, reporting)

IVDR: Quality of in-house devices (IH-IVDs)

(e.g. equipment, reagents, calibrators, control materials, software)

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

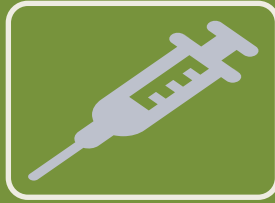


Key elements for LDT Regulation in EU

1. QMS
2. Risk-based approach for LDT classification
3. Risk management system
4. Evaluation and documentation 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!

VI. 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



Classification rules (7)

