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Dispositif de Diagnostic In Vitro -Paysage réglementaire en Europe

Journee Scientifique
Association des Responsables de Laboratoire de Suisse Romande

le 12 octobre 2021

Silvia Anghel, PhD– Senior Associate, IVD Head, Medidee Services

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Medical Devices and IVD Experts

Since 2013 Medidee offers consultancy services in Quality Assurance, Regulatory & Clinical Affairs and Digital Health supporting MedTech companies of all sizes, from idea to market

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Certification ISO 13485 – TUV Sud

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

TÜV SÜD Italia

CERTIFICATE

Nr. 50 100 15028

This is to certify that / *Si attesta che*

THE QUALITY SYSTEM OF
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REGISTERED OFFICE AND OPERATIONAL SITE:
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HAS BEEN FOUND TO COMPLY WITH THE REQUIREMENTS OF
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UNI CEI EN ISO 13485:2016

QUALITY SYSTEMS – MEDICAL DEVICES
SISTEMI QUALITÀ – DISPOSITIVI MEDICALI

THIS CERTIFICATE IS VALID FOR THE FOLLOWING SCOPE
QUESTO CERTIFICATO È VALIDO PER IL SEGUENTE CAMPO DI APPLICAZIONE

Consulting and training services on regulatory affairs, quality management and clinical affairs for medical devices and in-vitro diagnostics manufacturers

Erogazione di servizi di formazione e consulenza relativamente ad affari regolatori, gestione qualità e affari clinici per fabbricanti di dispositivi medici e di dispositivi per la diagnostica in-vitro

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For the Certification Body
Per l'Organismo di Certificazione
TÜV Italia S.r.l.

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Andrea Coscia
Direttore Divisione Business Assurance
2019-03-15

"THE VALIDITY OF THE PRESENT CERTIFICATE DEPENDS ON THE ANNUAL SURVEILLANCE EVERY 12 MONTHS AND ON THE COMPLETE REVIEW OF COMPANY'S MANAGEMENT SYSTEM AFTER THREE-YEARS"
"LA VALIDITÀ DEL PRESENTE CERTIFICATO È SUBORDINATA A SORVEGLIANZA PERIODICA A 12 MESI E AL RIESAME COMPLETO DEL SISTEMA DI GESTIONE AZIENDALE CON PERIODICITÀ TRIENNALE"

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Consultancy Services

Quality Assurance

- Implementation of Quality Management Systems (QMS) ISO13485, ISO15189 and ISO17025
- Coaching in Design & Industrialization
- Risk Management Activities
- Manufacturing Process Validation
- Software Validation
- Supplier Controls & Audits
- Internal audits
- Training

Regulatory Affairs

- Regulatory Pathway Development
- Preparation of Technical Documentation for CE Submission
- Preparation of 510(k), De Novo & PMA Submissions
- Presub Meeting with FDA
- National Registrations
- Management of Interactions with Notified Bodies & Competent Authorities

Clinical Affairs

- Clinical Pathway Development
- Writing CER /PER Evaluation Reports
- Risk / Benefit Assessment
- IVD Performance Studies
- Preparation and Submission of Clinical Investigations (Competent Authority, IRB, Ethical Committee)
- Clinical Investigation Monitoring and Audit
- Post Market Surveillance Support

Digital Health

- Support for the development of Software as a Medical Device
- Classification of software
- Cybersecurity assessment / ISO 27001 - IEC62443
- Support for compliance with Data Protection (GDPR – HIPAA)
- Support for compliance with Learning Machine, Artificial Intelligence
- Software Validation

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Medidee – Global Presence & Growing Organization

Team of **50+** scientists and engineers (50% PhD)

14 spoken and written languages

Switzerland
Lausanne (HQ), Olten

Germany
Munich, Lübeck, Stuttgart

Denmark
Copenhagen, Aarhus

Belgium
Charleroi

USA
Horsham PA

APAC
Philippines

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Topics

- Comprendre le paysage réglementaire actuel
- Comprendre la procédure d'évaluation de la conformité
- Aperçu des changements majeurs dans le paysage réglementaire européen
- Impact de cette transition réglementaire sur la disponibilité des dispositifs de diagnostic in vitro (IVD)
- Impact de cette transition réglementaire sur l'activité des laboratoire d'analyse médicale

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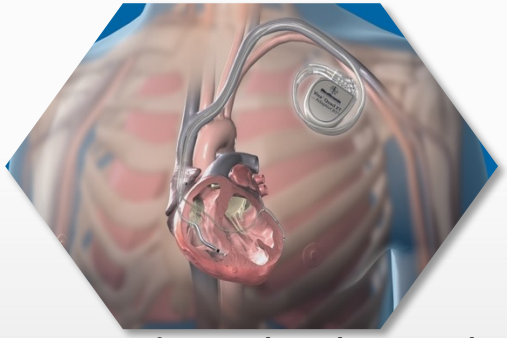
Medical Technologies – Main Categories

- **Medical Devices (MDs)** are products, services or solutions that prevent, diagnose, monitor, treat and care for human beings by physical means.



- **In Vitro Diagnostics (IVDs)** are non-invasive tests used on biological samples (for example blood, urine or tissues) to determine the status of one's health.

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EU Legislation

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EU Legislation – Historic Regulatory Framework

AIMDD	**MDD**	**IVDD**
Active Implantable Medical Device Directive	Medical Device Directive	In Vitro Diagnostics Device Directive
EC 90/385	EC 93/42	EC 98/79

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Directive vs Regulation in EU

EU - Directive

A "directive" is a legislative act that sets out a **goal** that all EU countries must achieve.

However, it is up to the individual member state **to decide how** by **transposition in national law.**

EU - Regulation

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EU Legislation – Medical Device & IVD Regulations

- **Inconsistencies** between national transposition of the directives
- Free trade **not any more guaranteed** within EU due to national «special cases»
- **Technology advancement** not properly covered
- **Political correctness** between member states prevailed over patient safety
- Notified Bodies had scopes **without having competences** required
- Notified Bodies did / were **not capable** to do their job
- Competent Authorities did not do their job, **no communication**

⇨ Public awareness and pressure triggered by PIP scandal

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EU Legislation – Historic Regulatory Framework

AIMDD

Active Implantable Medical Device Directive

EC 90/385

MDD

Medical Device Directiv

IVDD

In Vitro Diagnostics Device Directive

EC 98/79

Replaced by
“Medical Device Regulation”
MDR – EU 2017/745
and
“IVD Regulation”
IVDR – EU 2017/746

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Directive vs Regulation in EU

EU - Directive

A "directive" is a legislative act that sets out a **goal** that all EU countries must achieve.

However, it is up to the individual member state **to decide how** by **transposition in national law**.

EU - Regulation

A "regulation" is a **binding** legislative act.

It must be **applied entirely across the EU**.

A regulation **replaces national law**.

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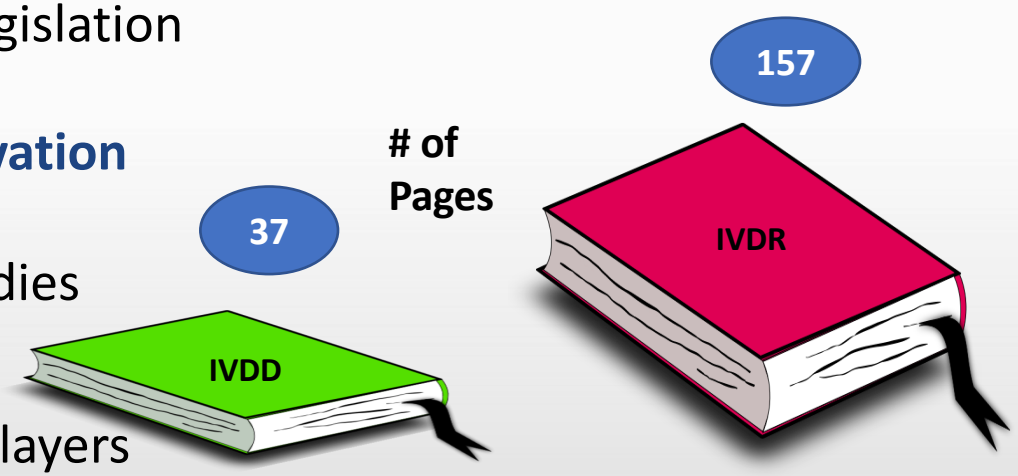
EU Legislation – Medical Device & IVD Regulations

- **One single text** applicable over all member states – no national interpretations or “special cases”
- **Eliminate** grey zones in current legislation
- Catch up with **technological innovation**
- Enhance **control** over Notified Bodies
- **Ensure competence** of different players
- Improve **transparency** and **information exchange** between stakeholders



⇨ All for promoting the objective of safety

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EU Legislation – Single Market

- The **single European Market** comprises 27 Member States of the European Union, the European Economic Area – EEA (Iceland, Liechtenstein and Norway) and through bilateral treaties, Switzerland
- **Free movement of goods** is one of the cornerstones of the single European Market

- To enable this concept of free movement, **three** conditions must be met:
  1) **General Safety and Performance Requirements (GSPRs)** for the products involved must be defined
  2) **Methods** must be established to describe how **product compliance** with the GSPRs is addressed
  3) **Mechanisms** to **supervise** and **control** the actions of all Economic Operators and others involved in the manufacturing and distribution of the products must be created

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EU Legislation – Accord de Reconnaissance Mutuelle avec CH

Loi Federale sur les medicaments et les dispositifs medicaux

Ordonnance sur les dispositifs médicaux (ODim)

Art 4 - Requirements for medical devices
Art 5 – Classification
Art 8 – Conformity marking
Etc.

Art 46

Procedures pour l'evaluation de la conformité

The law

The ordinance

Apply EU Rules

EC 93/42, Annex I-XII
EC 90/385, Annex I-XII
EC 98/79 Annex I-XII

⇨ CE Mark is also valid in Switzerland

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EU Legislation – Transposition into Swiss Law

2017/745 (MDR)

Harmonization of the CH legislation (ODim)

INSTA – Institutional Agreement

- **MD_Swixit** – Third Country as of 26.05.2021 !
- **Status for IVD**
  - under IVDD Mutual Recognition Agreement is valid
  - under IVDR it will depend on the future negotiations

ODim: Ordonance sur les dispositifs medicaux

MRA: Accord de Reconnaissance Mutuelle

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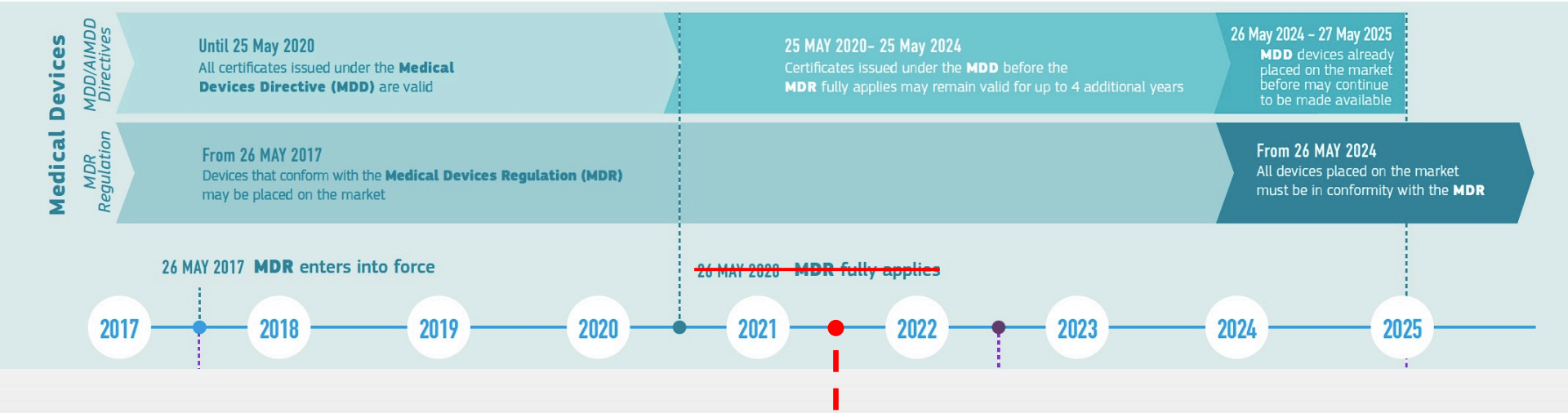
MDR Implementation –Timeline



Date of Application MDR postponed to 26 May 2021

MDR is already applicable

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2020.130.01.0018.01.ENG&toc=OJ:L:2020:130:TOC

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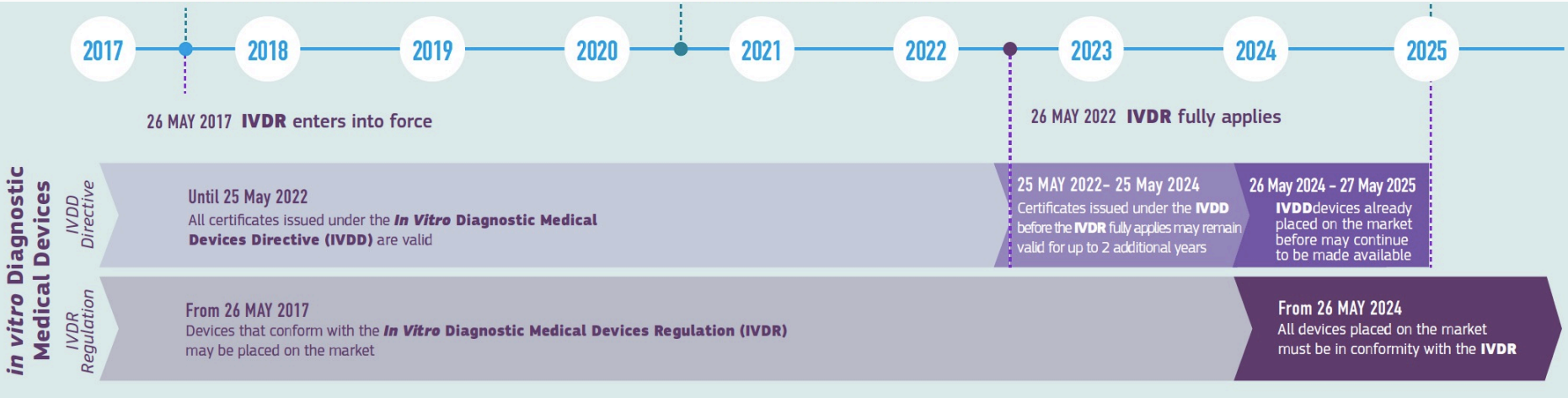
IVDR Implementation – Timelines



Source: https://ec.europa.eu

Date of Application 26 May 2022

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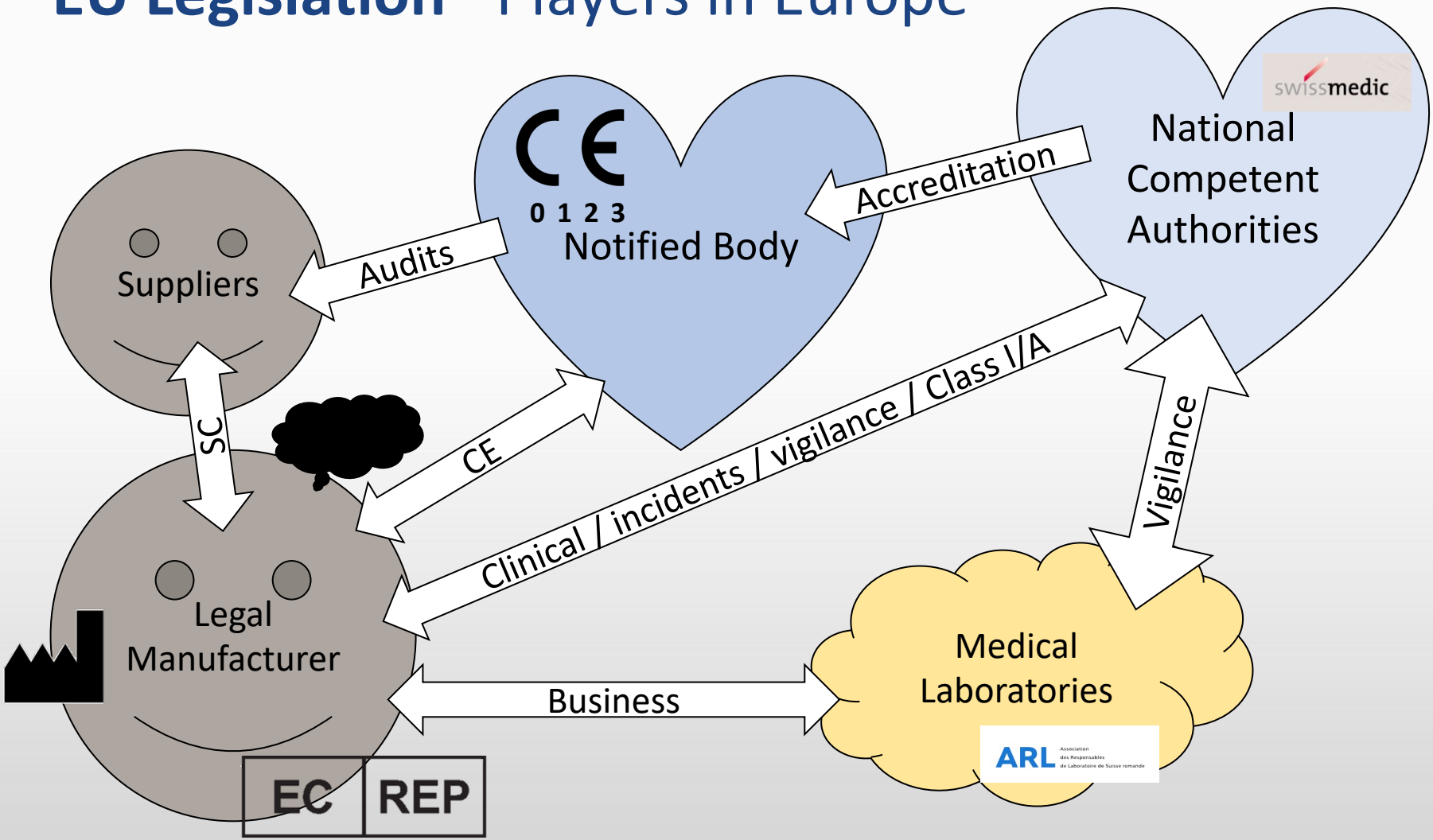
EU Legislation– Players in Europe



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EU Legislation – CE Marking and Conformity Assessment

- **Conformity assessment** means the process demonstrating whether the requirements of the Regulation relating to a device have been fulfilled;

- **The Conformity Assessment is the Review of Tech Doc AND QMS (ISO 13485)** to check that the product meet the applicable EU requirements:
  - safe and performs as **intended** by the manufacturer
  - **conforms to the *GSPR (ERs under IVDD)***

- **Notification vs Certification**

CE

ISO 9001 & ISO 13485
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Conformity Assessment – Notified Body

- In the EU, the Notified Body is an organization that has been accredited by a Member State to assess whether a product meets defined requirements, conformity with with the **general safety and performance requirements**.

- **Assessment can include inspection and examination of a product, its design and manufacturing process, as well as Technical Documentation and Quality Management System**.

- Check of the quality and relevance of **clinical data** (including demonstration of a **favourable risk/benefit ratio** for the patient)

- Formal **regulatory aspects**:
  - Labelling
  - List of Applicable Standards
  - Declaration of Conformity

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EU Legislation – CE Marking and Conformity Assessment

- **Manufacturers** are responsible to carry out the **conformity assessment**, set up the **technical file**, issue the **EU declaration of conformity**, and **affix the CE marking** to a product

- Only then can a product be **traded on the EU market**

CE

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Declaration of Conformity– Conformity Assessment

Declaration of Conformity

EU Technical Documentation assessment certificate

EU Quality Management system certificate

CE 0123

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IVD classification –98/79 EC Directive

-> positive lists (Directive)

Dir. 98/79 EC (IVDD) Annex II

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IVDD Classification, examples

Other	Self test	List B	List A
low risk	low to moderate risk	moderate risk	high risk
Instruments Specimen receptacles All tests not covered by list A, B and Self Test (including devise intended for diagnosis of cancer)	Pregnancy self-test Cholesterol self-test	reagent products for determining blood group per anti-Duffy reagent products for detection of toxoplasmosis reagent products for determining PSA tumoral marker blood glucose self-test	reagent products for determining blood group per ABO system reagent products for detection of HIV, Hepatitis B, C and D

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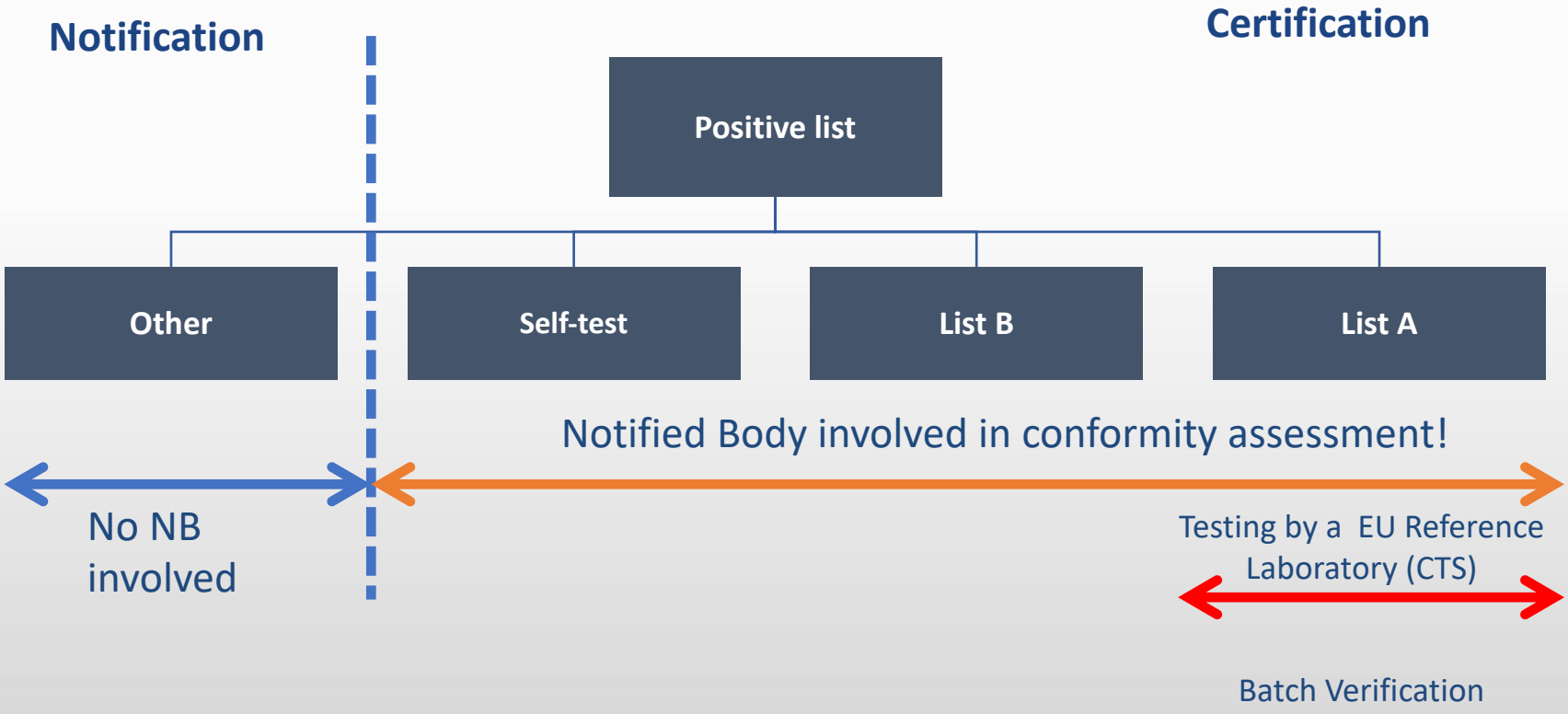
In Vitro Diagnostic Device –Placement on the market under IVDD



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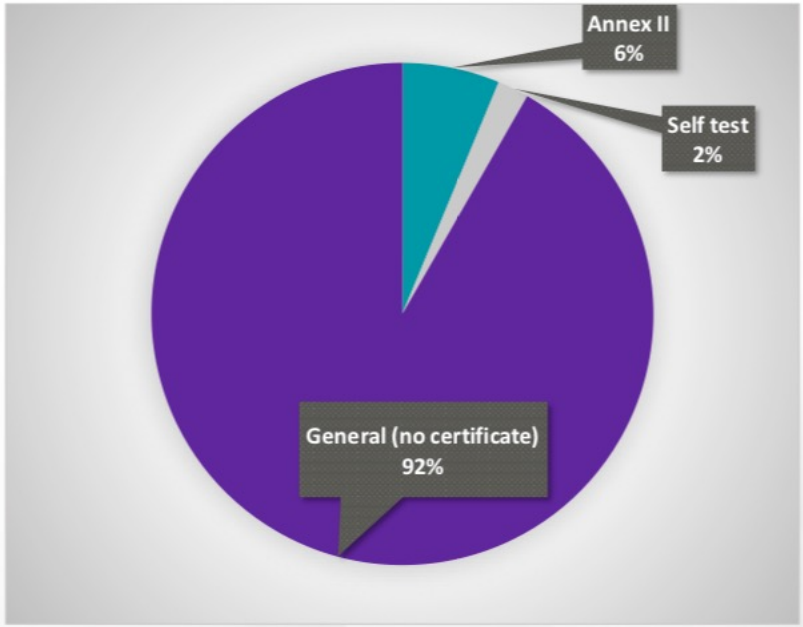
IVDR Implementation – Timelines

The number of devices which have a Notified Body certificate issued by category (IVDD)

	Number of devices
Annex II certificate	2.501
Self-test certificate	801
General (no certificate)	36.542
Total	**39.844**

92% of all IVDs currently do not need to have a Notified Body certificate under IVDD

Only 8% of all IVDs currently have a Notified Body certificate under IVDD and could potentially make use of the 'grace period'* until May 2024



*transitional provisions under IVDR Art 110(3)

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Placement of a product on the market – IVDR

Concept

Review of Tech Doc AND QMS to check that:

- IVD : safe and performs as intended by the manufacturer
- conforms to the *General Safety and Performance Requirements*

primarily responsibility of manufacturer

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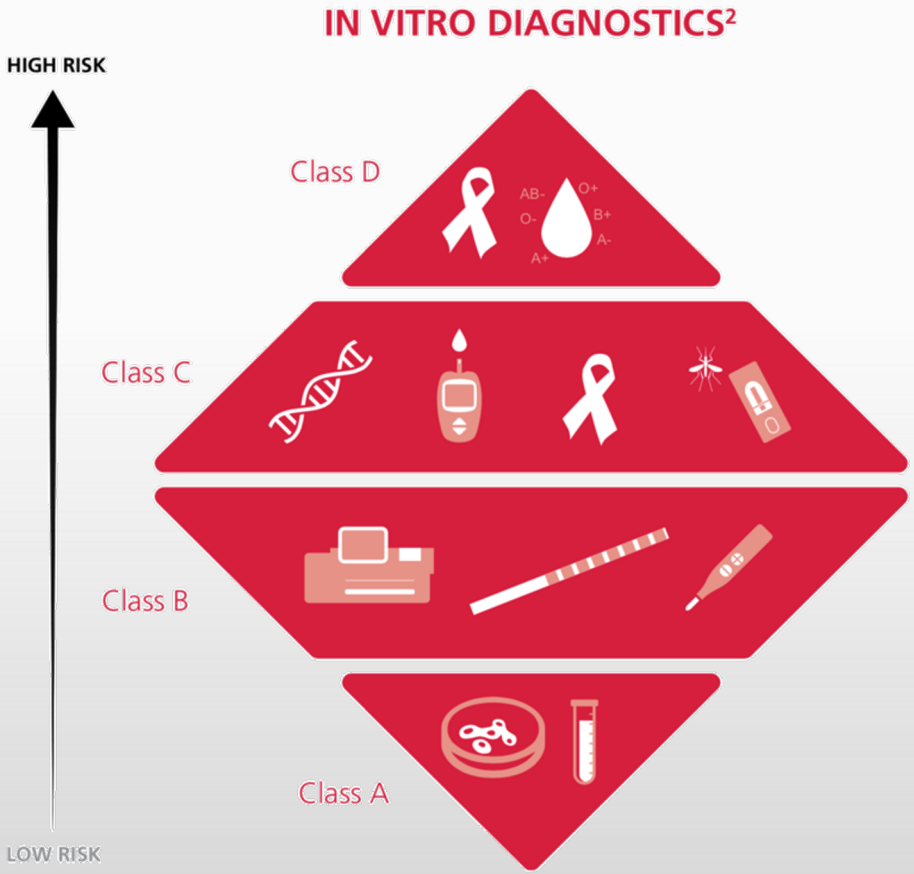
IVDR– New Risk Based Classification



Source: Eucomed

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Medical Device & IVD – Intended Purpose

'**intended purpose**' means the use for which a device is intended according to the …

- label
- instructions for use; and
- promotional or sales materials / statements

and

- as **specified** by the manufacturer in the **clinical evaluation/performance evaluation**
- based on the **claims** made for the device (**claims need to be substantiated throughout the clinical evidence**)

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In Vitro Diagnostic Device (IVD) – Intended User & Environment

- Of particular importance for Self-tests and Point of Care Test (POCT)

The characteristics and performances of the device shall be specifically checked in the event that they may be affected when the device **is used for the intended use under normal conditions**:

➢ **clinical clinical evidence related to user and environment**

(GSPR 9.4)

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IVDR Product Classification – Classification

- **Classification will depend upon intended use** i.e., screening claims and the level of risk to the patient and the public (taking into account the likelihood of harm and the severity of that harm)

- The notion of **Point of Care, Companion Diagnostic** and **Software** were also introduced in the IVDR

- **Identical devices may be classified differently if they are to be used for different diagnostic purposes**.

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IVDR Product Classification – Example of the link between the Intended Purpose and Classification

- The company “STM” developed and market in Europe a blood test intended for diagnosis of syphilis. The test is intended for use in a medical setting and be performed by a health professional.

Class C

- The company decided to extend the intended purpose of the test to the screening of blood donners.

Class D

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IVDR Classification, examples

Class A	Class B	Class C	Class D
low risk	low to moderate risk	moderate risk	high risk
Instruments General Reagents Specimen receptacles	Measurement of electrolytes /homeostasis Helicobacter pylori Autoantibodies	Cancer Companion diagnostics Genetic testing Self-tests (except an exemption list Class B)	reagent products for determining blood group per ABO system reagent products for detection of HIV, Hepatitis B, C and D Diagnosis of Covid infection

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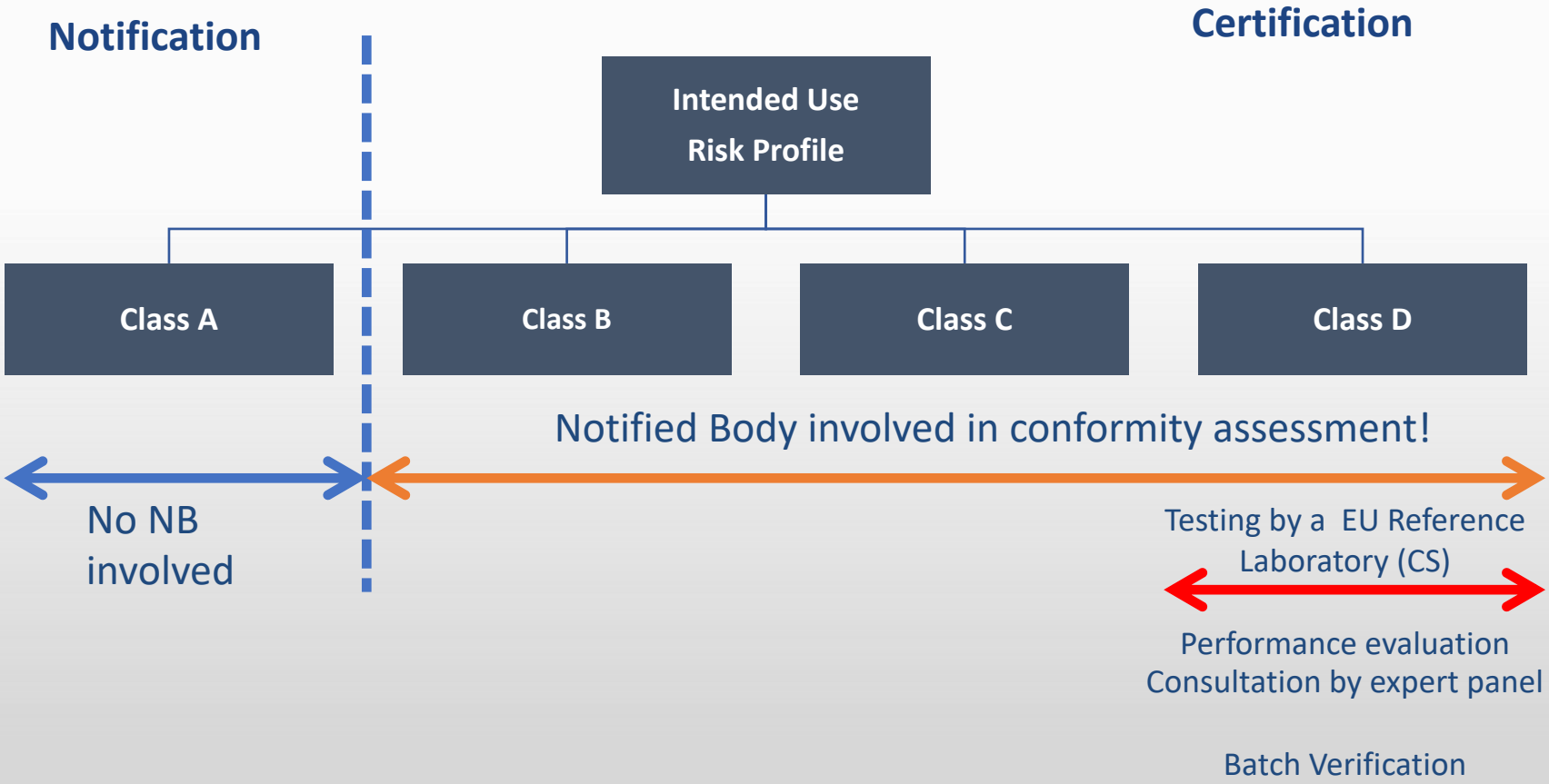
In Vitro Diagnostic Device –Conformity Assessment under IVDR



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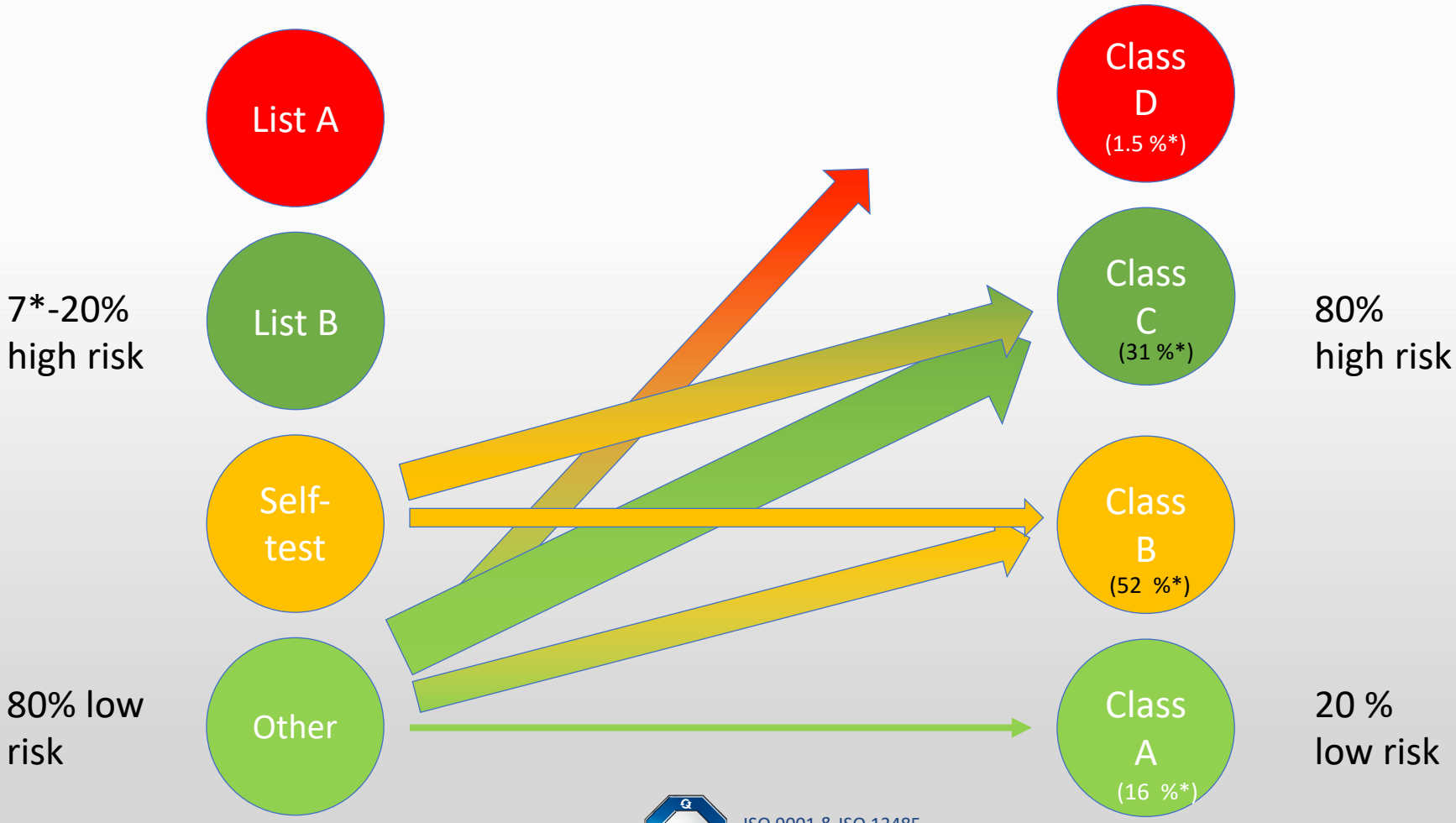
IVD– Major Changes introduced by the new Regulations

98/79 EC | **Reg.EU 2017/746**



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*Dutch National Institute for Public Health and Environment, 2018

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Device classification under IVDR

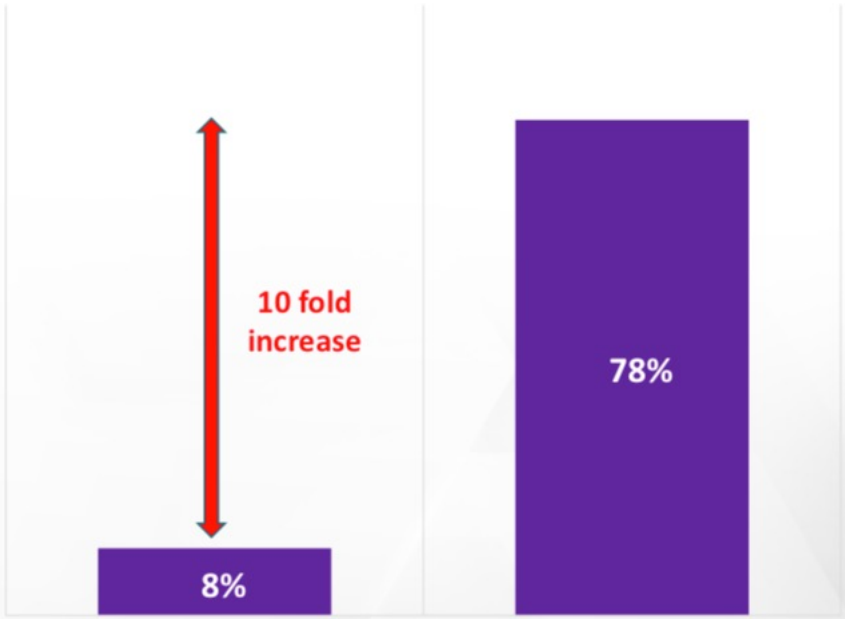
The number of devices that need a Notified Body certificate

	Number of devices that need a certificate
IVDD	3.302 (8%)
IVDR	24.346 (78%)

The percentage of devices requiring a NB certificate climbed from 8% to almost 80% of the total devices from IVDD to IVDR.

This can be read as ~10-fold or 736% increase in the number of IVDs needing at least 1 Notified Body certificate* from IVDD to IVDR

* All IVDs in class D, C, B and A (sterile) need to be covered by a QMS certificate. In addition, individual devices in Class D, for near patient testing, for self-testing and which are companion diagnostics need in addition technical documentation assessment certificate *see slide 9*
Only Class A (non-sterile) do not need to be covered by a Notified Body certificate.



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MedTech Europe
from diagnosis to cure

➢ 80 / of the IVD devices will requier a NB certificate

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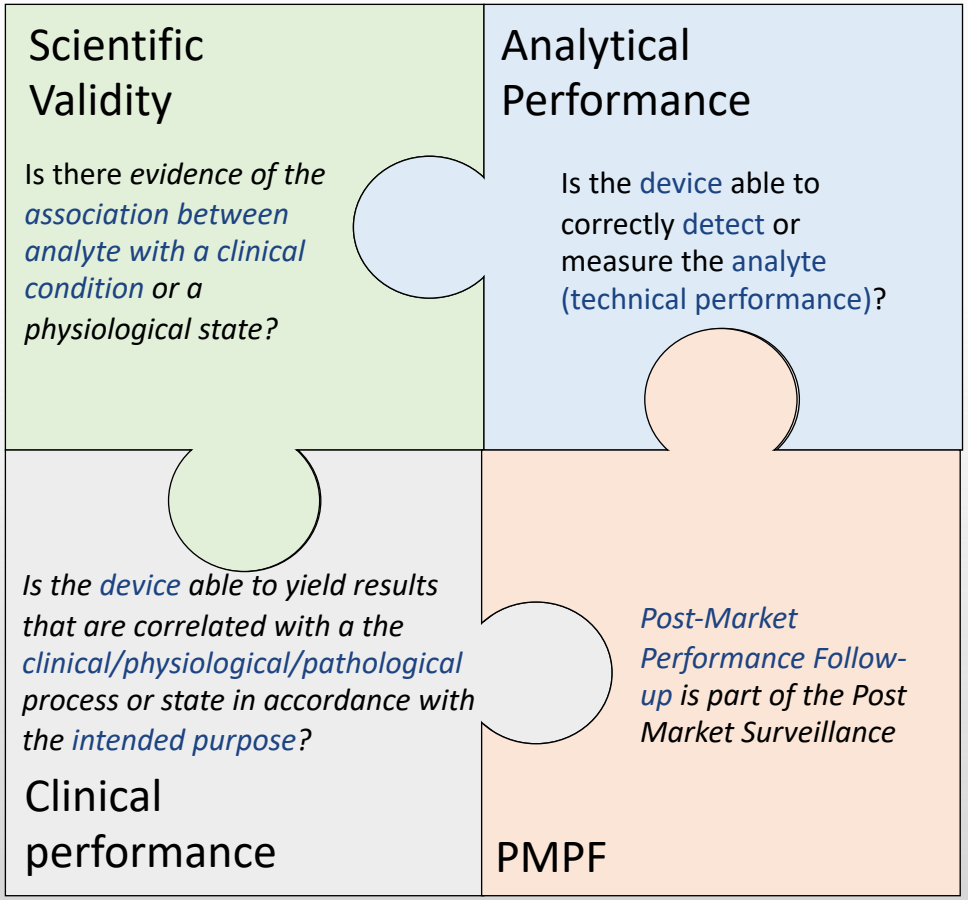
Data expectation - Clinical Evidence and Performance Evaluation Report (PER)



+ Usability (POCT)
& Risk Management

Useful guidance: MDCG 2020-1 Guidance on Clinical Evaluation/Performance Evaluation of MD Software

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Data expectation - How should I address the Clinical Evidence?

	Establish & Standardized Tests	Establish & Non-Standardized Tests	New Tests
Example	NaCl; blood gases; biochemical identification of microorganisms	cardiac markers; tumor markers (CEA), cell markers (CD4)	new cancer maker
Scientific Validity	yes	yes	yes
Analytical Performance	yes	yes	yes
Clinical Performance	No	yes/no	yes

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IVDR Implementation – NB Bottleneck

Body type ▲	Name ▲	Country ▲
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 0459	GMED SAS	France
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany

https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=35

Regulatory Act	Actual Number
IVDD 98/79/EC	22
IVDR 2017/746	**6**

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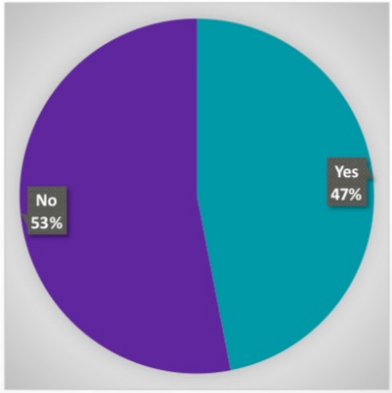
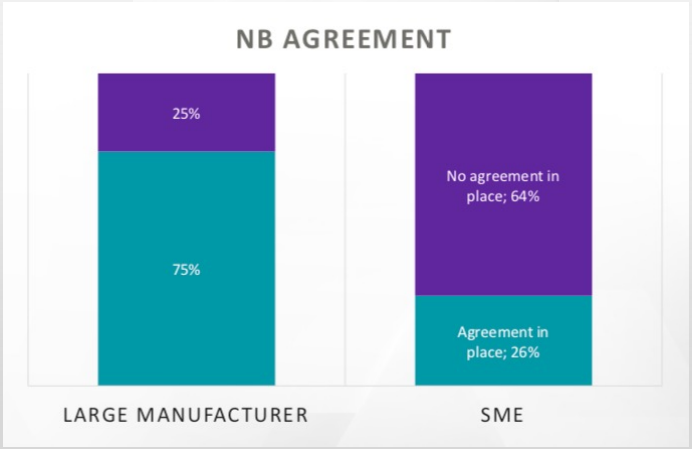
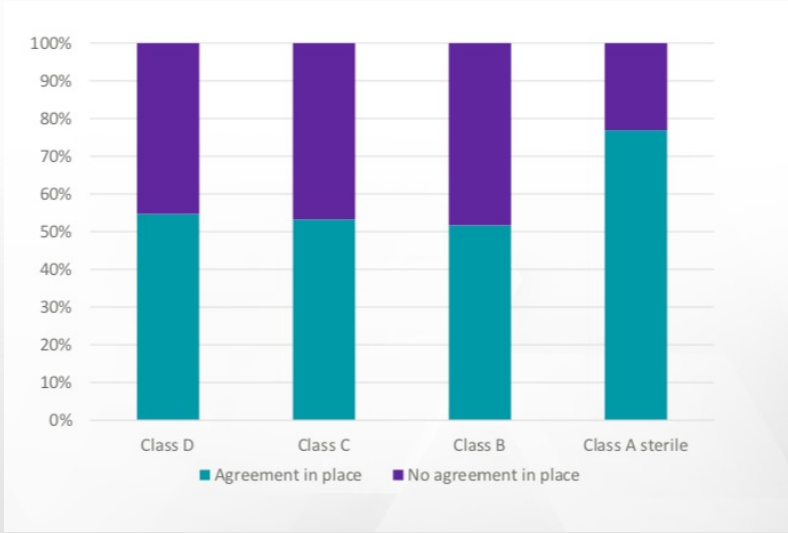
IVDR application – NB Bottleneck: current status

Companies with NB agreements in place







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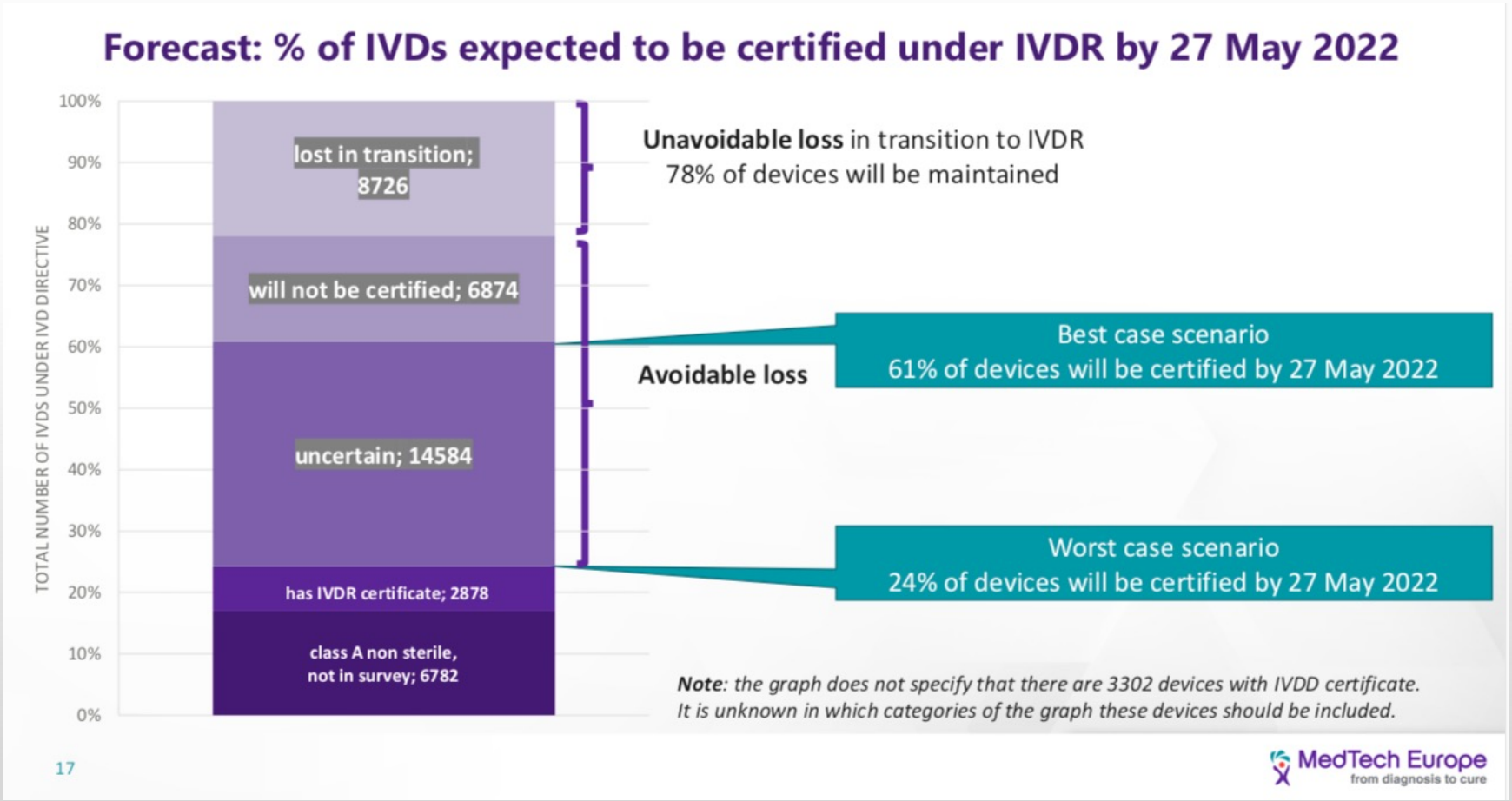
IVDR application – Consequence on the availabilities of products by May 27, 2022



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IVDR application – Consequence on the availabilities of products from May 27, 2022

- **Short term**
  - ➢shortage on available IVDs (play smart and increase stocks)
- **Long term**
  - ➢Increase financial burden to place and keep on the market IVD devices, could be transferred on the users
  - ➢Large pharma companies will win the game/small companies (niche market) may not survive
  - ➢Niche products may be stopped
  - ➢May slowdown the R&D

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IVDR application – Increase safety and information: EUDAMED

- **EUDAMED** stands for "**European Database for Medical Devices**" is operated by the European Commission and serves to centralize all relevant information on medical devices on the EU market and to ensure traceability and transparency

- Public Access to the following information:

  - Information about the device registered
  - The related certificates of conformity, their scope and validity period
  - Clinical investigations related to the device (partial access)
  - Summary of Safety and Performance (SSP)
  - Manufacturer incident reports and field notice for vigilance activities (partial access)
  - Results of the Post Market Surveillance assessment (partial access)

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IVDR Implementation – Postponement of the IVDR?

- MedTech Europe called for a pause on the IVDR transition 09.07.2020
- The European Association for Medical Devices of Notified Bodies (Team-NB) issued a position paper, 25.11.2020
  - Current situation is **not optimal** for the application of the IVDR

  Alternate Options
  - Longer grace period to include moderate/ low risk devices (class B) and low risk devices (A sterile) as for class I devices MDR
  - Postponement of DoA of the IVDR to 2023 ?
- The European Commission (EC) unveiled on June 2021 its new joint implementation and preparedness plan for the European Union's In Vitro Diagnostic Regulation (IVDR) and acknowledge the situation

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In house devices_The Article 5.5

IVDs **manufactured and used in-house** :

- a device that is manufactured only **within a health institution established in the EU** (health institutions outside EU cannot use the in-house exemption)
- **is used within the same institution**
- **address, 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 CE marked device available on the market.**

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In house devices_The Article 5.5

Health institution includes**:**

- hospitals
- laboratories and
- public health institutions

The health institution does not cover establishments such as gyms, spas, wellness and fitness centres.

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In house devices_The Article 5.5

When this article apply?

- Manufacturing a device from raw material (eg: antibodies)/parts/components
- Combination of products with a medical purpose where the products
  - are not CE-marked
  - The combination is not in line with the intended use as claimed by the manufacturer
- Significant modification of a medical device (IVD) (eg: extended/change of the intended use, design change…MDCG 2020-3)

Examples:

- A PCR master mix allowing detection of a new merging disease (all raw material is ordered but are not IVD products)
- An in-house developed software that qualifies as IVD (or MD) and is used in house

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In house devices_The Article 5.5

- The demonstration to GSPR remains mandatory
- Multiple conditions apply, in particular an accreditation with EN ISO 15189 and implementation of a QMS that allows traceability of the manufacturing and Post Market Surveillance (similar devices)
- **Country specific restrictions may exist, need to consult the competent authority or national legislation!**
- **Notification to National Competent Authority is expected**

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Take Home Message

- The new IVD Regulation (IVDR) is applicable starting on **May 26, 2022**
- The classification under the new Regulation will **upgrade 80% of the IVDs to a conformity assessment process that requires the involvement of a Notify Body**
- **Starting on May 26, 2022, all the IVDs that are currently classified as "General" need to obtain a valid certificate under IVDR –** need to verify the availability of IVD used in each laboratory after May 2020
- At short term, due to the lack of available Notify Body, we may face a shortage of IVD on he market
- At long term, it may increase the costs related to R&D and may slow down the development of devices that target niche markets
- Health institutions are allowed to developed their in-house devices , however multiple conditions apply, and the normally the notification to the Competent Authority is expected (Article 5.5 IVDR)

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