# The New EU IVD Regulation 2017/746:
## consequences & opportunities for Laboratory Medicine

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IFCC
International Federation of Clinical Chemistry and Laboratory Medicine

# Disclosures

- None related to the content of this lecture.

# New EU IVD Medical Device Regulation

A. Background
B. Rationale for new legislation
C. IVDR key changes
D. EU Regulatory Framework
E. Preparing the transition for IVDR compliance of CE-IVDs and LDTs
F. Conclusions


# A. Background: what exactly has changed?

## EU Medical Device Legislation

**three Medical Device Directives**

* Active Implantable MDD
  - Directives 90/385/EEC + 2007/47/EC
* Medical Devices MDD
  - Directives 90/385/EEC + 2007/47/EC
* In Vitro Diagnostic MDD
  - Directive 98/79/EC

**MDR**

***Regulation 2017/745***

***Regulation 2017/746***

**IVDD** ⇨ **IVDR**

# Purpose of Regulatory Requirements in Healthcare

The purpose of MDR/IVDR legislation is to **regulate the trade in medical devices and 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.

# MDR 2017/745 and IVDR 2017/746

These **Regulations lay down rules concerning**

- ✓ the placing on the market,
- ✓ making available on the market,
- ✓ or putting into service

of medical devices/ In Vitro Diagnostic medical devices (= medical tests) for human use and accessories for such devices in the Union.

LAWS EXPLAIN **WHAT TO DO/ NOT HOW TO DO!!**

The **Regulations also apply to performance studies** concerning such medical devices/ In Vitro Diagnostic medical devices and accessories conducted in the Union.

# Difference between Directive and Regulation?

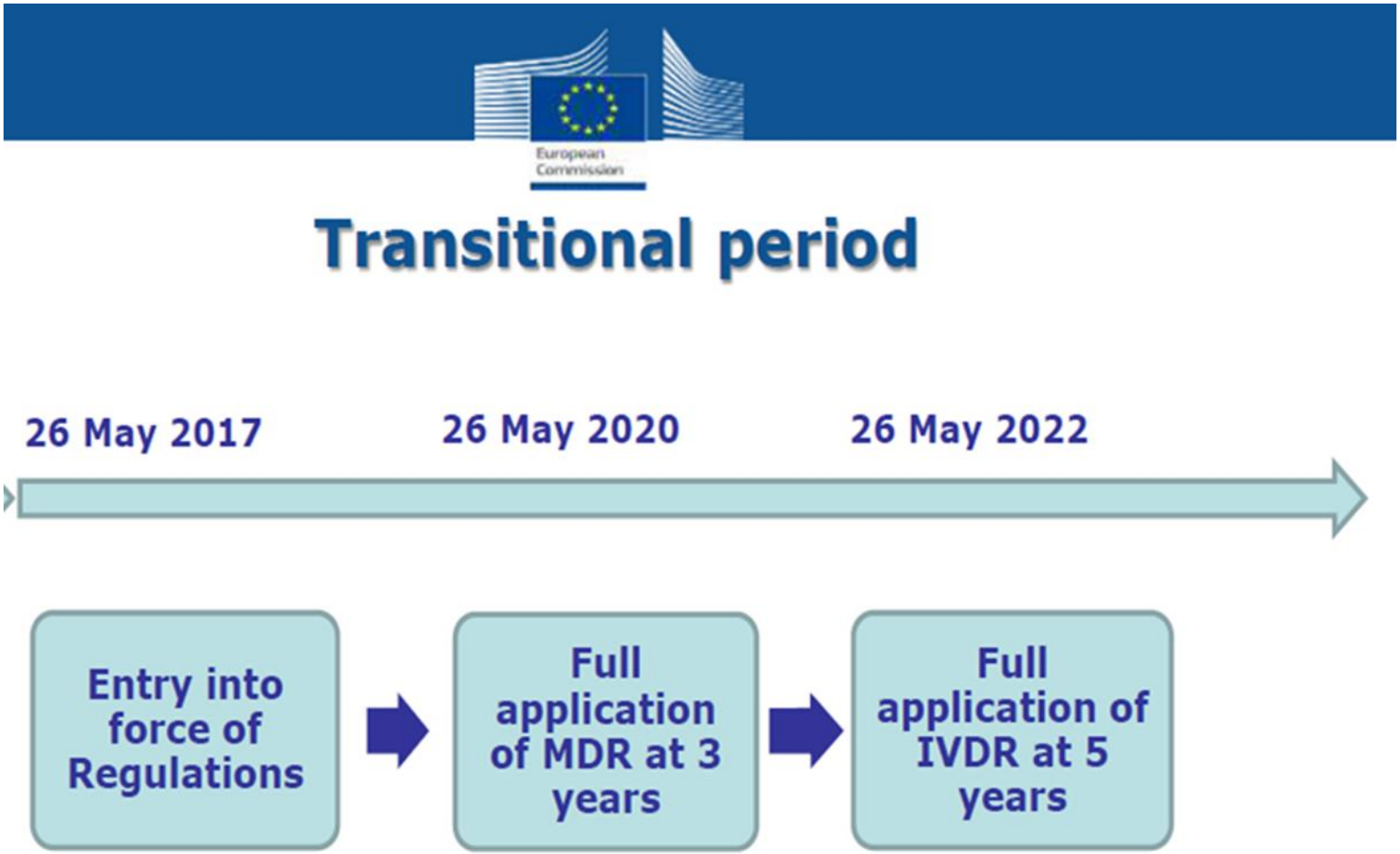
## EU Directive:

- Applicable to all Member States.
- Sets certain aims, requirements and concrete results that must be achieved in every Member State.
- Sets a process for it to be implemented by Member States.
- National authorities **must create or adapt their legislation to meet these aims** by the date specified in a given Directive.

## EU Regulation:

- **Immediately applicable and enforceable by law in all Member States**.
- As good practice, Member States issue national legislation that defines the competent national authorities, inspections and sanctions on the subject matter.

# Timelines for full application



# B. Rationale for changes in legislation?

### Hip Replacement Recalls

In 2010, metal on metal (MoM) hip replacements were recalled due to high failure rates as the MoM device wearing down led to metal particles entering the bloodstream and soft tissues

### Breast Implant Crisis

In 2012, unexpectedly high number of women were diagnosed as suffering from ruptured breast implants leading to the breast implant crisis. The crisis took place as the French firm had been manufacturing implants using industrial grade silicone. The situation was made worse by poor record keeping, with women unable to find out whether they had received these implants or not

These separate incidents highlighted the need for strengthening of the EU Medical Device Directives.

# Process of market access of IVDs under the current IVDD

## Risk-based categorization of the IVDs in TWO LIMITATIVE LISTS List A and List B.

IVDs mentioned in List A are the highest risk devices and require the most extensive examination (scrutiny) of a notified body.

- ✓ Examples of IVDs that are on List A are products for the determination of blood groups AB0, Human Immunodeficiency Virus (HIV), Human T-cell leukemia virus (HTLV) or hepatitis.
- ✓ Examples of IVDs on List B are blood glucose meters and products for the detection of chlamydia, rubella and trisomy 21.

For devices on list B a less extensive assessment by notified bodies is required.

For devices for **self-testing**, a notified body has a **LIMITED ROLE** to check the aspects related to self-testing only.

The IVDs not on List A or B, and which are not devices for self-testing, are referred to in this report as '**IVD other**', and do **NOT** require assessment by a notified body.

# IVDD shortcomings

Because of the use of limitative lists with higher risk IVDs in the IVDD, **newly developed tests** not mentioned in these two lists, **by default do not require scrutiny by a notified body. This is irrespective of their risk**.

- ✓ An example of such a development was a test for Creutzfeldt-Jakob disease (CJD).

# Rationale for changes in legislation?

## Current IVDD 98/79/EC

a. Established harmonized standards to demonstrate conformity to Essential Requirements;
b. Defined Conformity Assessment procedures;
c. Facilitated the organization of Notified Body and Competent Authority oversight and market surveillance.

**Worked well and has helped to create a Single Market for IVDs in Europe!**

**However: not capable of regulating all new technical and medical developments!**

a. New developments: genetic testing and companion diagnostic devices;
b. Need to better align with international guidelines;
c. Lack of control over high risk “in house” tests.

# Focus on IVD Regulation 2017/746

Regulation (EU) 2017/746 on in vitro diagnostic medical devices

&

repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Official Journal of the European Union, L 117, 5 May 2017

http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2017:117:TOC

All Member State National laws have to be rescinded.
**New Regulation is nearly 400 pages long –existing IVD Directive was under 100 pages**
Lots of changes.

# Overview of IVDR Chapters & indication of relevant Articles

| Chapter | Title | Relevant articles |
|---|---|---|
| I | Introductory provisions incl. Scope and Definitions | |
| II | Placing on the market, putting into service, CE Marking, Economic Operators, Free movement | 5.5 (requirements for LDTs) |
| III | Identification and Traceability of Devices | |
| IV | Notified Bodies | |
| V | Classification and Conformity Assessment | |
| VI | Clinical Evidence, Performance Evaluation and Performance Studies | 56-77 (clinical evidence) |
| VII | Post Market Surveillance, Vigilance and Market Surveillance | 78-87 (post-market surveillance) |
| VIII | Cooperation between Member States | |
| IX | Confidentiality, Data Protection, Funding and Penalties | |
| X | Final Provisions | |

# C. IVDR key changes

I. Scope and (Re)Classification;

II. Clinical Evidence Requirements;

III. Notified bodies and Conformity Assessment;

IV. Post-market Surveillance;

V. UDI & data upload in Eudamed database;

VI. IVD-specific issues: “in house” tests or LDTs

# I. Scope and Classification

## 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..

See Article 2 of EU IVDR 2017/746

# IVD Medical Device Regulation – DEF. & SCOPE

... solely or princip**for the purpose of providing information** on one or more o

SCOPE ENLARGEMENT
Including high risk "In House" tests

(a) Concerning a physiological or f state;
(b) Concerning congenital physical or ment nts;
(c) Concerning the **predisposition** to a medical condition or a disease;
(d) To determine the safety and compatibility with potential recipients;
(e) To **predict** treatment respons or reactions;
(f) To **define** or monitor therape tic measures.

Companion Diagnostics

Genetic testing

# IVDR (Re)Classification

- Major changes to how IVDs will be classified
- Will be a **RISK-RULE BASED SYSTEM** using **G**lobal **H**armonisation **T**ask **F**orce (GHTF) classification rules
- **Impacts 80-90% of tests**: **QUANTUM LEAP!**

# Classification rules

- **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.

# IVD Device Classes

**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.

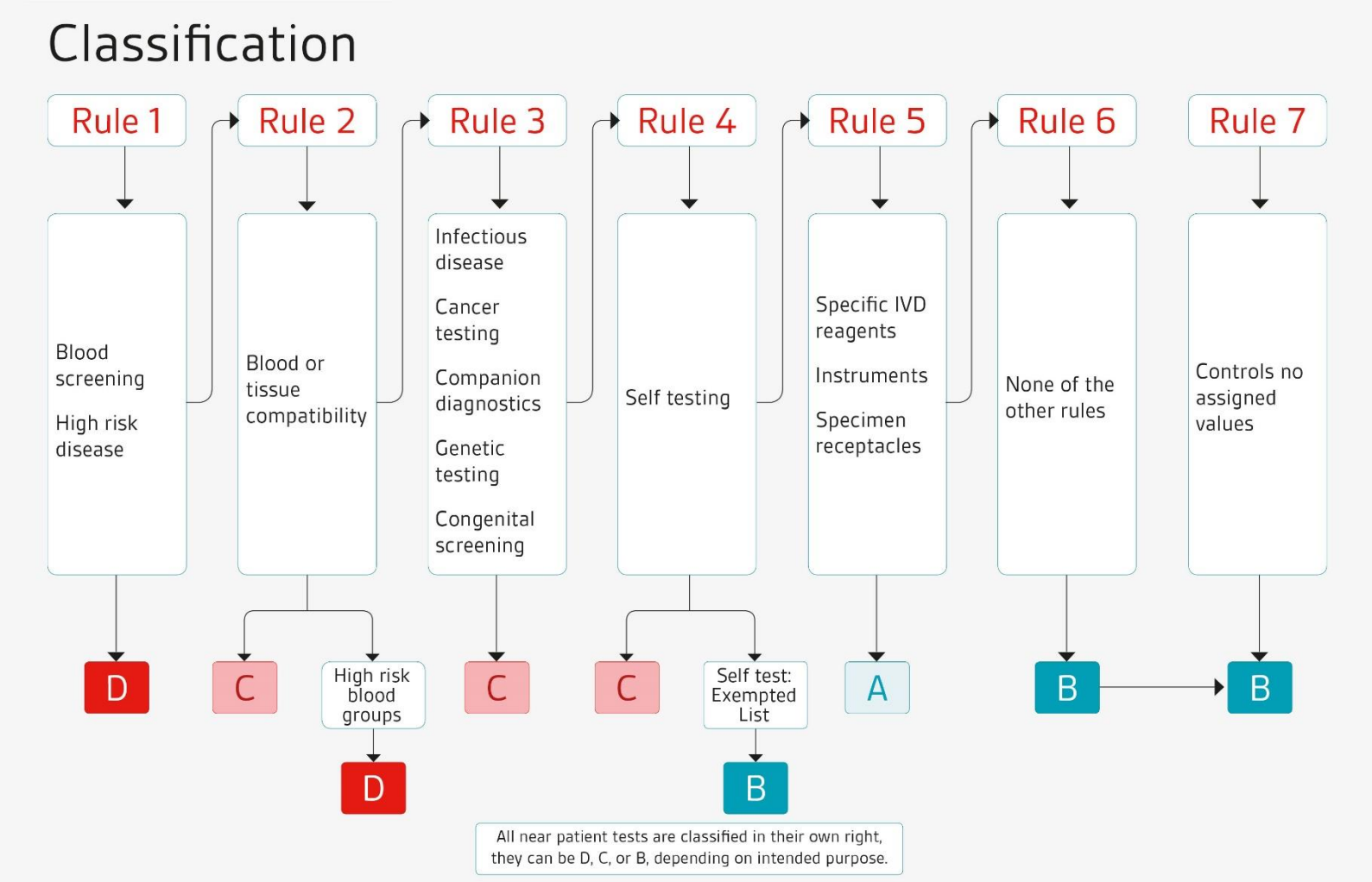
**B**

- Medium risk for individual patients
- e.g. blood chemistry, pregnancy tests, etc.

**A**

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

# New IVDR: risk-based classification of IVDs



# Process of market access of tests under the new IVDR

The new European regulation on *in vitro* diagnostic medical devices (IVDR) introduces **a rule-based classification system**. Annex VIII of the IVDR addresses seven classification rules.

Using these classification rules, an IVD can be assigned one of **four risk classes (A-D)**, A being the lowest risk class and D the highest.

The classification rules take into consideration factors such as purpose of the test (e.g. assessment of suitability of blood for transfusion or monitoring the stage of a disease), the risk of propagation, the nature of the disease or agent (e.g. cancer or sexually transmitted agent), and the type of specimen (i.e. blood or urine) to establish the risk class.

Devices classified in **class A** can be **self-certified** by the manufacturer.
For IVDs in **Class B, C or D**, assessment by a **notified body** is required for market authorization.

# Impact of (re)classification on existing products

Compagnies **cannot 'grandfather' existing products**

- ✓ All existing products must be reclassified!
- ✓ Need to perform a gap analysis on existing data.
- ✓ May need to undertake additional performance studies.

Companies will **need to notify end users** of any products that may leave the supply chain **in time** for alternatives to be sourced – lab medicine staff should be aware of this possibility.

# Impact of (re)classification on ….

**Cost** –Notified Body services are paid for by the manufacturer.

**Shortage of Notified Bodies** –Manufacturers who don't already use a NB need to start the process of identifying one now.

**Product portfolios** may need to remove some products from the market –if they become uneconomical to supply OR if their performance will not meet criteria under the Regulation.

Some products may face a **big change in classification** (e.g. syphilis tests – currently self-certified but will become Class D).

# Reclassification impact on volumes: IVDD categories versus IVDR risk classes

A representative sample of all IVDs registered in the registration database of the Dutch Central Information Unit on Health Care Professions (CIBG) was classified according to the classification rules of the IVDR. The complete dataset consisted of 5390 entries.

Percentage of IVDs requiring a notified body in order to obtain market authorization increases from 7% to 84% (Class B-D in IVDR classification).

*Table 1a: distribution of database entries over IVDD categories and notified body approval*

| | Registered database entries (n = 946) | |
|---|---|---|
| **Authorisation procedure** | **IVDD categories, % (n)** | |
| Self-certification | **IVD other** | 93.1 (881) |
| Notified body approval required | **List A** | 0.9 (9) |
| | **List B** | 4.2 (40) |
| | **Self-test** | 1.7 (16) |

*Table 1b: distribution of database entries over IVDR risk classes and notified body approval*

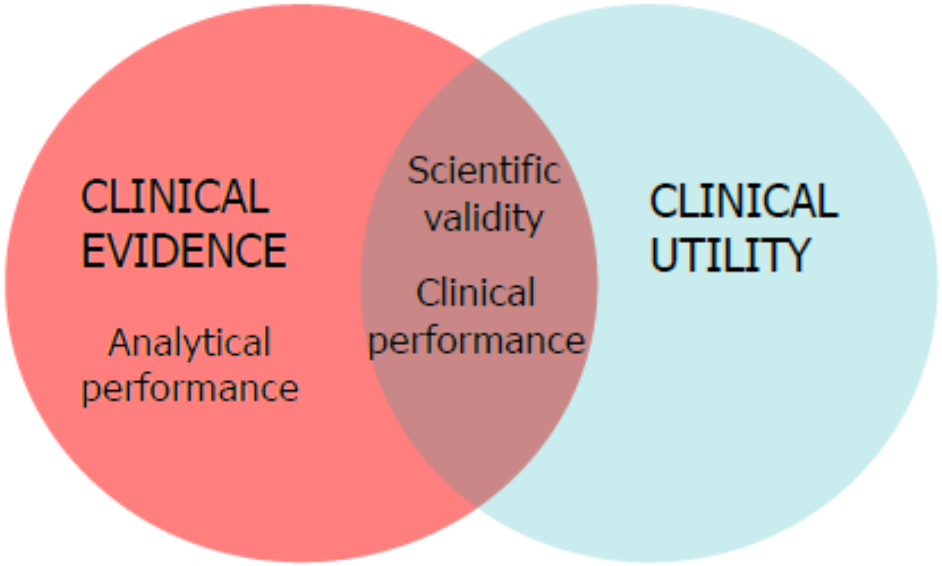
| | Registered database entries (n = 946) | |
|---|---|---|
| **Authorisation procedure** | **IVDR classes, % (n)** | |
| Self-certification | **A** | 15.9 (150) |
| Notified body approval required | **B** | 51.7 (489) |
| | **C** | 31.0 (293) |
| | **D** | 1.5 (14) |

Source: RIVM Letter report 2018-0082

# II. 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.**



# Clinical Evidence Requirements

**Definitions:**

- **Analytical performance** – the ability of an IVD medical device to correctly detect and measure a particular analyte.

- **Clinical performance** – the ability to yield results that relate to a particular clinical condition or physiological state for the intended use, the target population and intended user.

- **Scientific Validity** – the association of an analyte to a clinical condition or physiological state.

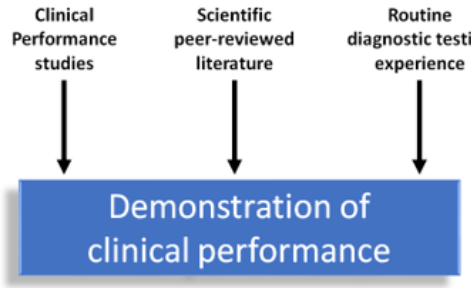
# Clinical Evidence Requirements

**New requirement with major impact**:

… **demonstration of compliance** with the **general safety & performance requirements** should be **based on Clinical Evidence**

….**based on data on scientific validity and analytical performance and clinical performance of the device**…

- Sourced from performance studies;




- Updated throughout the product's lifecycle;
- Generated through a Performance Evaluation Plan and collated into an annual Performance Evaluation Report.

# Tools developed by EFLM WG on Test Evaluation

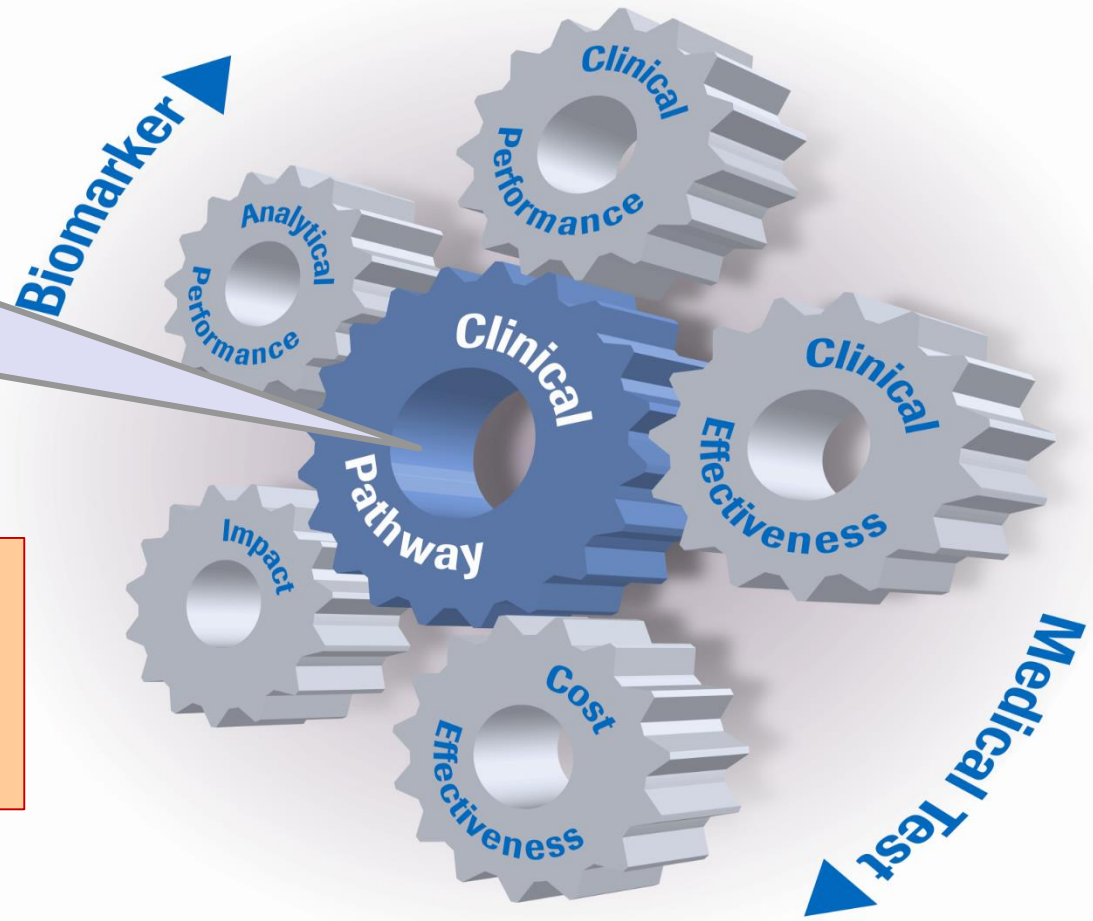
## Cyclical framework for the evaluation of *in vitro* medical tests


Horvath AR et al., CCA, 2014

**Key components of the test evaluation process are driven by the clinical need of using a test in the clinical pathway.**

# The Test Evaluation Cycle

**Is there an unmet clinical need and is there an effective intervention?**




**Unmet clinical need:**
**any missing or inadequately performing component of a clinical pathway.**

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Biomarker development targeting unmet clinical needs
Monaghan P et al, CCA, 2016; 460: 211-9.

# IVDR Article 56

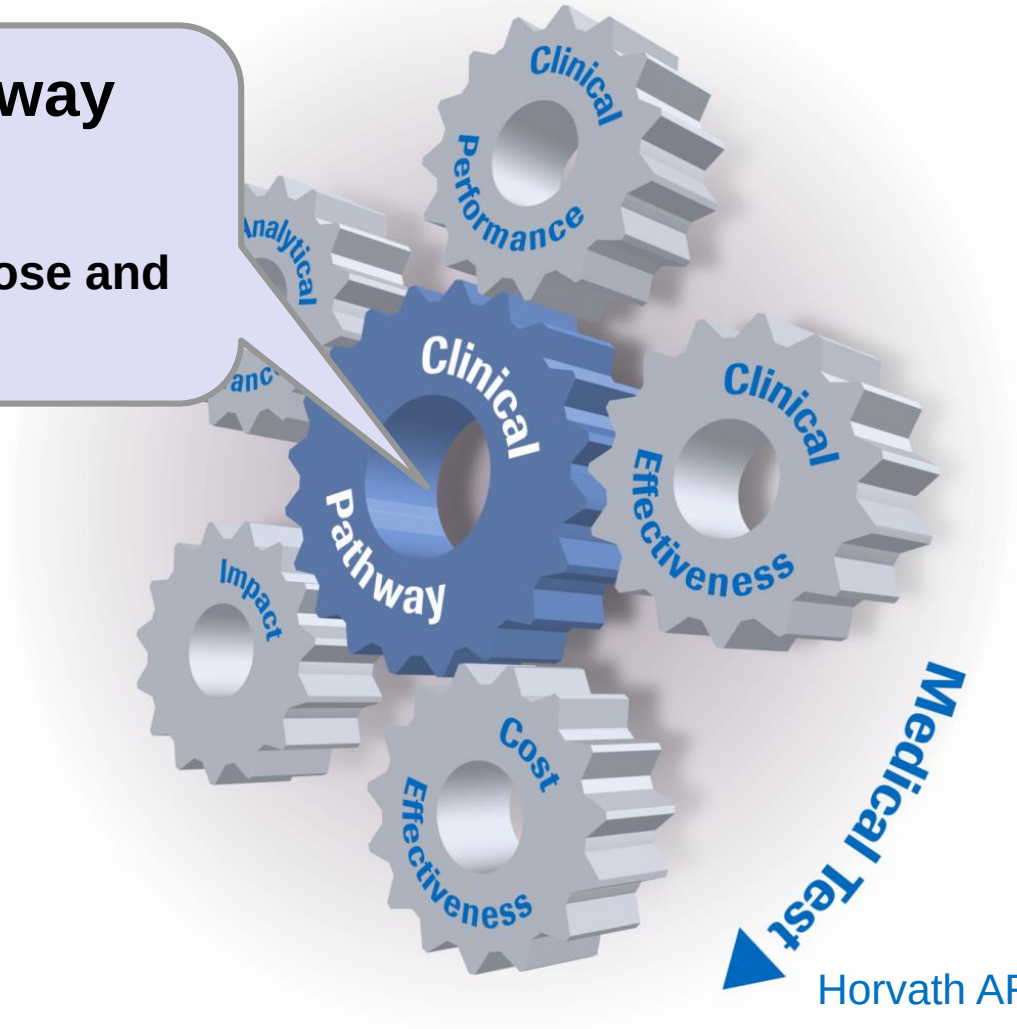
The ***clinical evidence*** shall be such as to scientifically demonstrate, by reference to the state of the art in medicine, that the intended clinical benefit(s) will be achieved and that the device is safe.

The ***clinical evidence*** derived from the performance evaluation shall provide scientifically valid assurance, that the relevant general safety and performance requirements …are fulfilled, under normal conditions of use.

# ‘Reference to the state of the art’ and ‘normal conditions of use’

**Clinical pathway mapping:**

**What is the purpose and role of the test?**

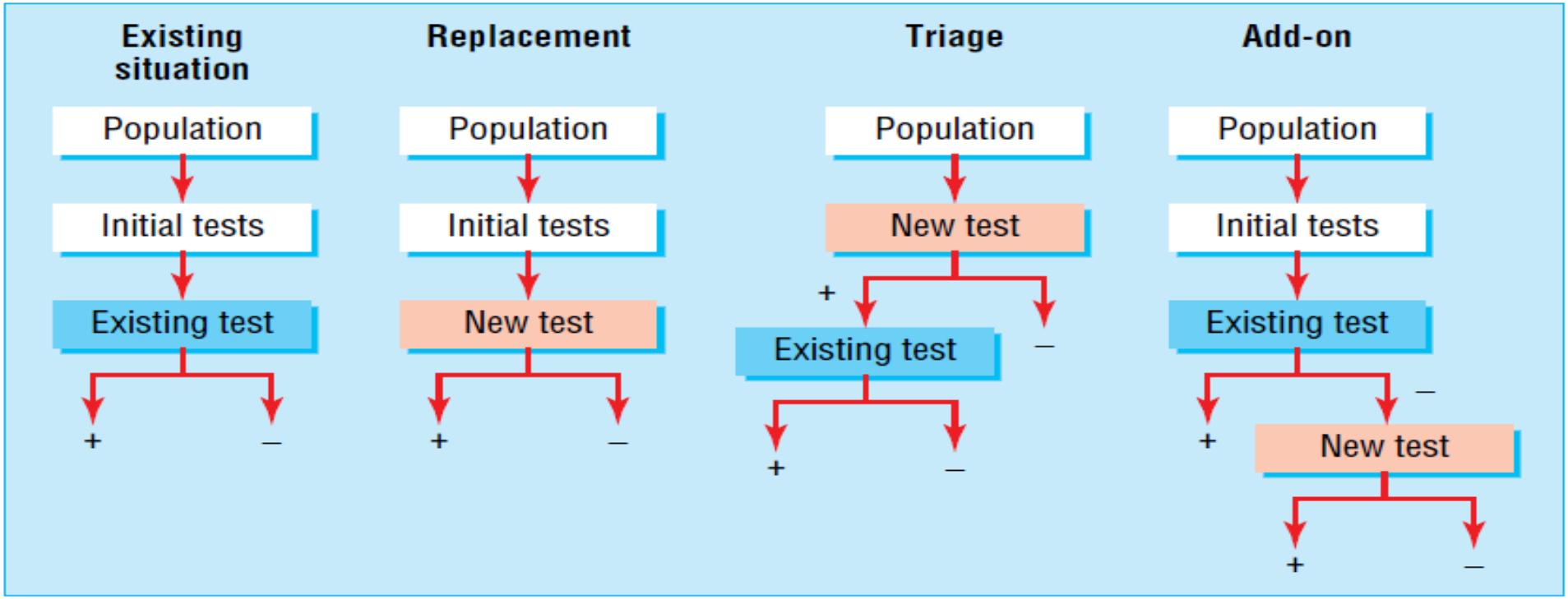



Horvath AR et al., CCA, 2014

# Test role and purpose in the clinical pathway

Comparative accuracy: assessing new tests against existing diagnostic pathways

Patrick M Bossuyt, Les Irwig, Jonathan Craig, Paul Glasziou




*Bossuyt et al. BMJ 2006*

# Key messages

**Before a new test is fully evaluated, the**

- **unmet clinical needs,**
- **intended purpose (screening, diagnosis, monitoring, etc.)**
- **role (add on, replacement, triage),**
- **population,**
- **healthcare setting in which the test is intended to be used,**
- **condition that is intended to be managed with the use of the test,**
- **procedures for evaluating these, and**
- **potential final outcomes of testing**

**must be clearly defined.**

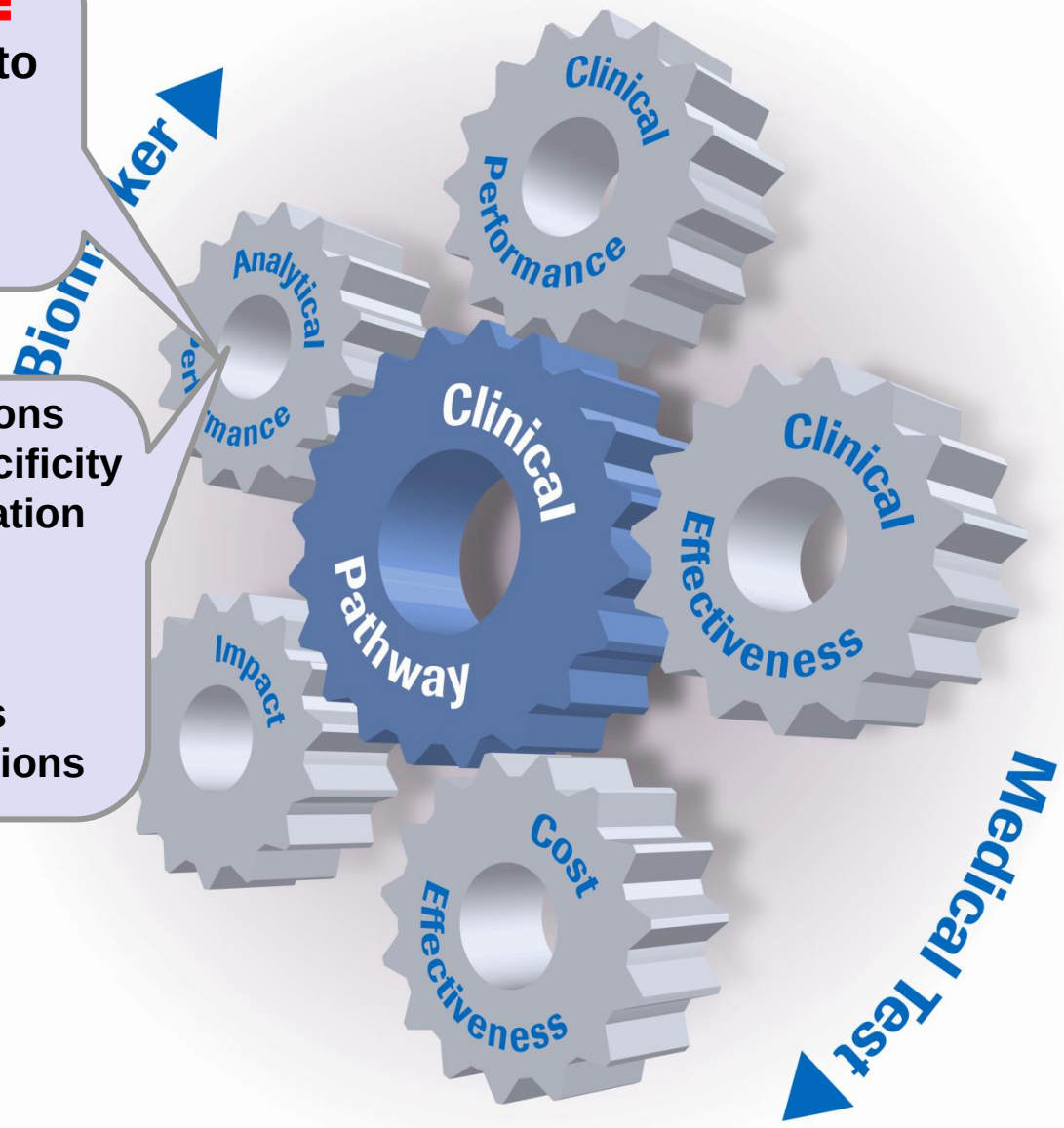
**All the above are best mapped out by drawing the clinical pathway**

*Bossuyt, 2010*

# The Test Evaluation Cycle

**IVDR Article 2 (40):**
The ability of a device to correctly detect or measure a particular analyte.

- preanalytical considerations
- analytical sensitivity/specificity
- limit of detection/quantitation
- measurement range
- linearity
- metrological traceability
- imprecision and trueness
- interferences cross-reactions

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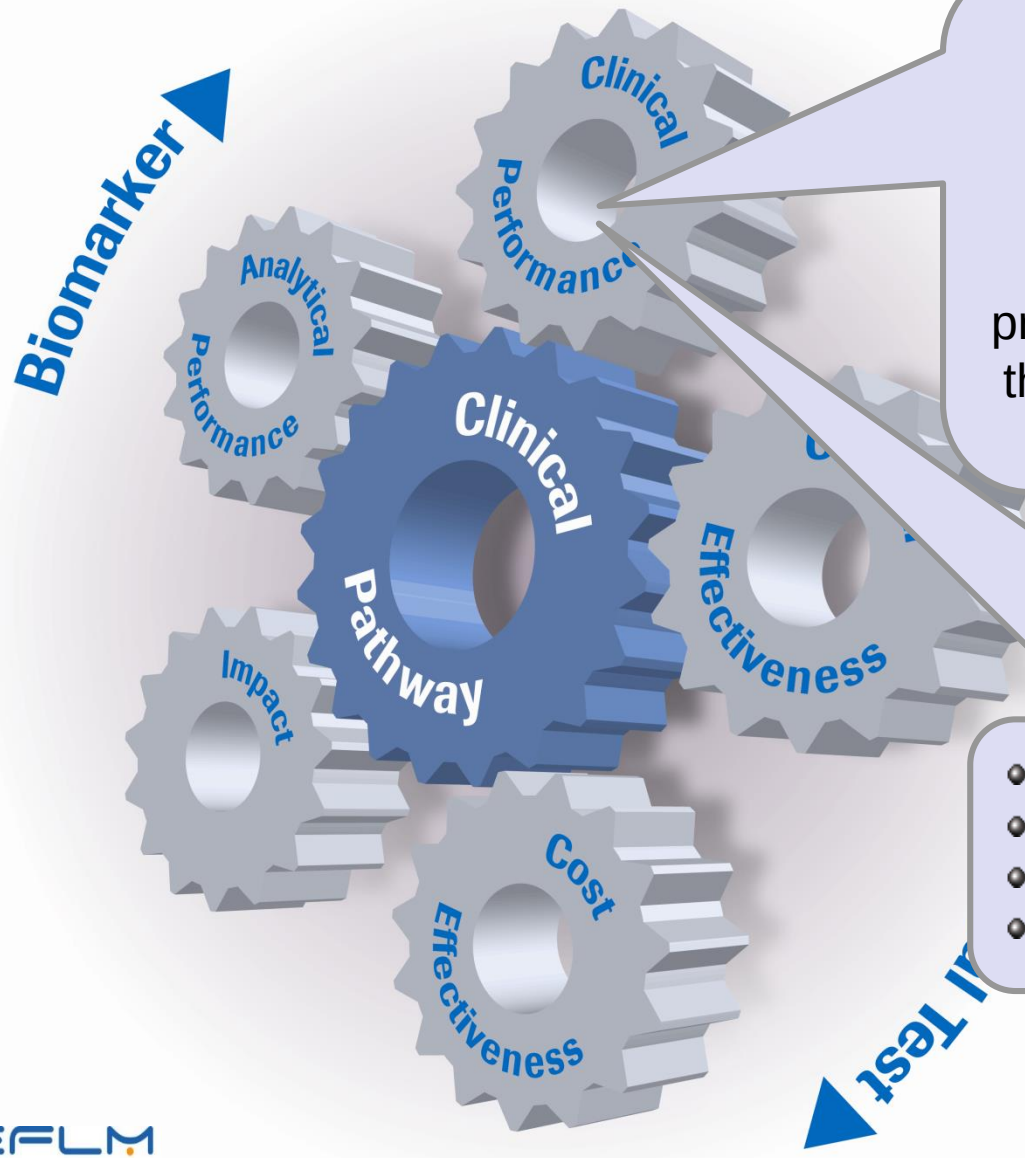
# Key messages

## Analytical performance specifications

- should reflect clinical needs
- can be based on 3 different models:
  - 1/ outcomes
  - 2/ biological variation
  - 3/ state-of-the art;
- should be set at a level that achieves net health benefit for patients at reasonable costs;
- should be tailored to the purpose and role of the test in a well defined clinical pathway;
- should be commensurate with the impact of the laboratory test on subsequent medical decisions and actions

*Clin Chem Lab Med 2015; 53(6): 841–848*

# The Test Evaluation Cycle




**IVDR Article 2 (41)**

the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user

- **How well does it work in practice?**
- **In what subset of patients?**
- **Is it really better than Old Bore®?**
- **How do alternative tests compare?**

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# Impact of Clinical Evidence requirements?

## Which IVDs are affected?

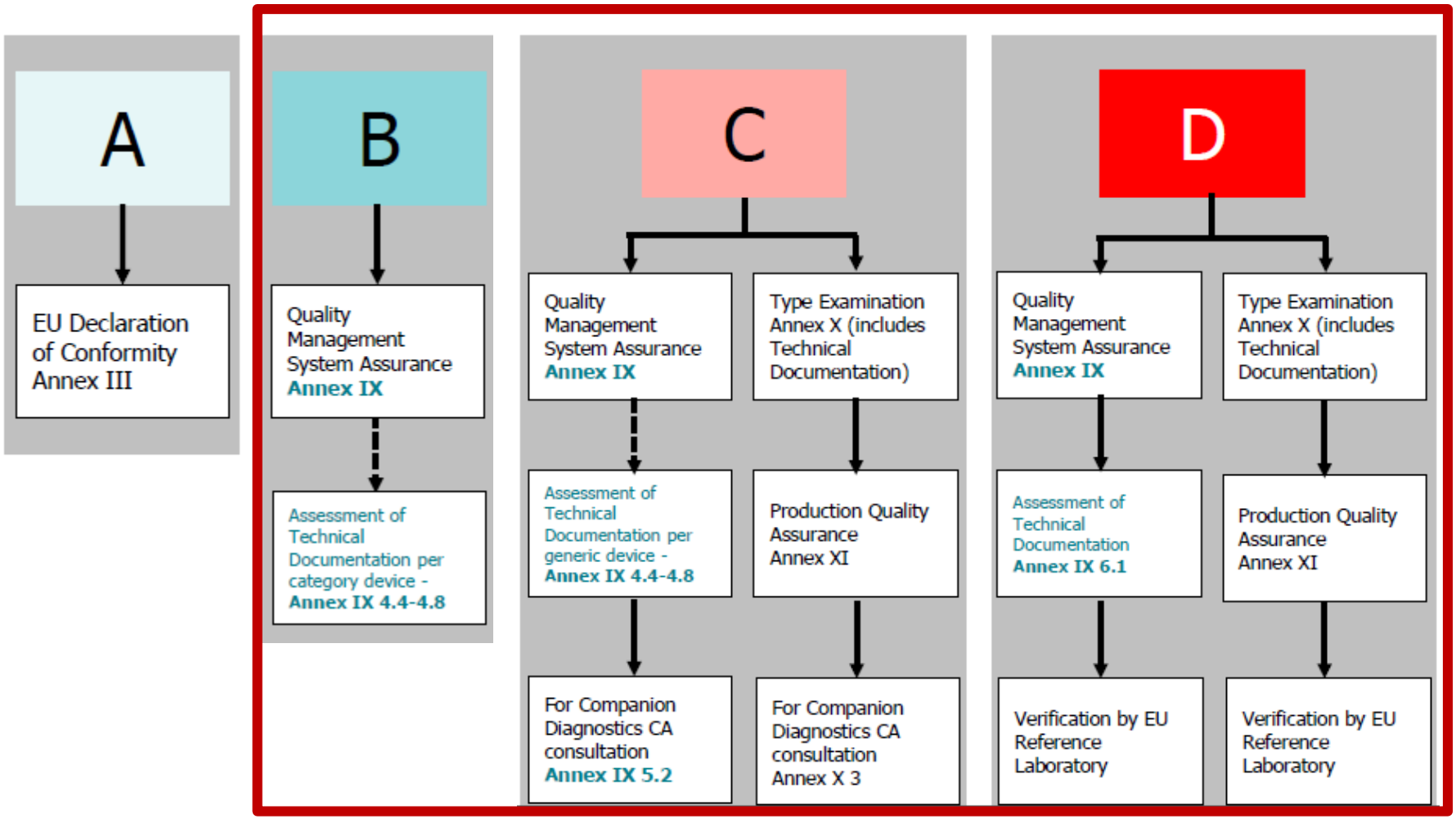
1. Clinical Evidence applies in principle to all IVDs.

2. However, impact of Clinical Evidence will be very different for established analytes (all information will be in the literature) vs. novel analytes.

3. Clinical evidence requirements are **DRIVEN BY RISK** of incorrect result, degree of innovation, novelty, degree of variability of the subject population and disease state and the intended user of the device.

4. The requirements are similar to international IVD development and regulatory standards (TGA, FDA, SFDA).

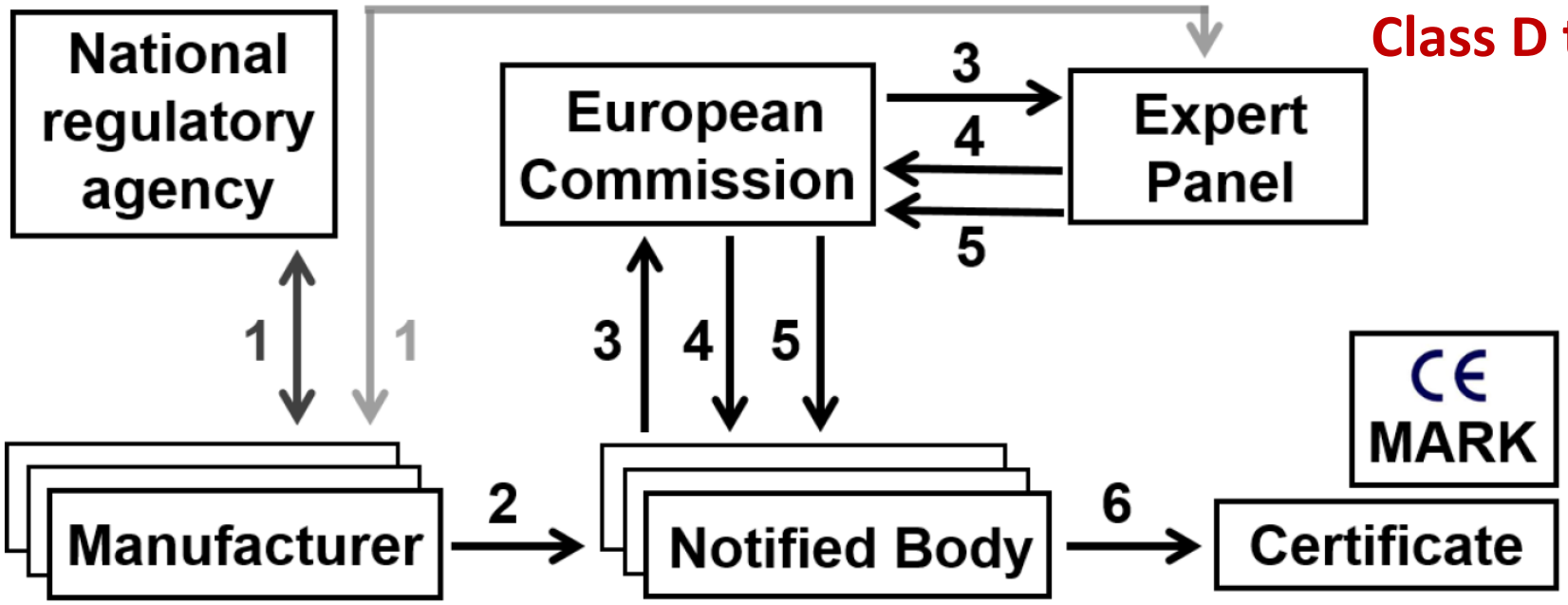
# III. Conformity Assessment by Notified Bodies



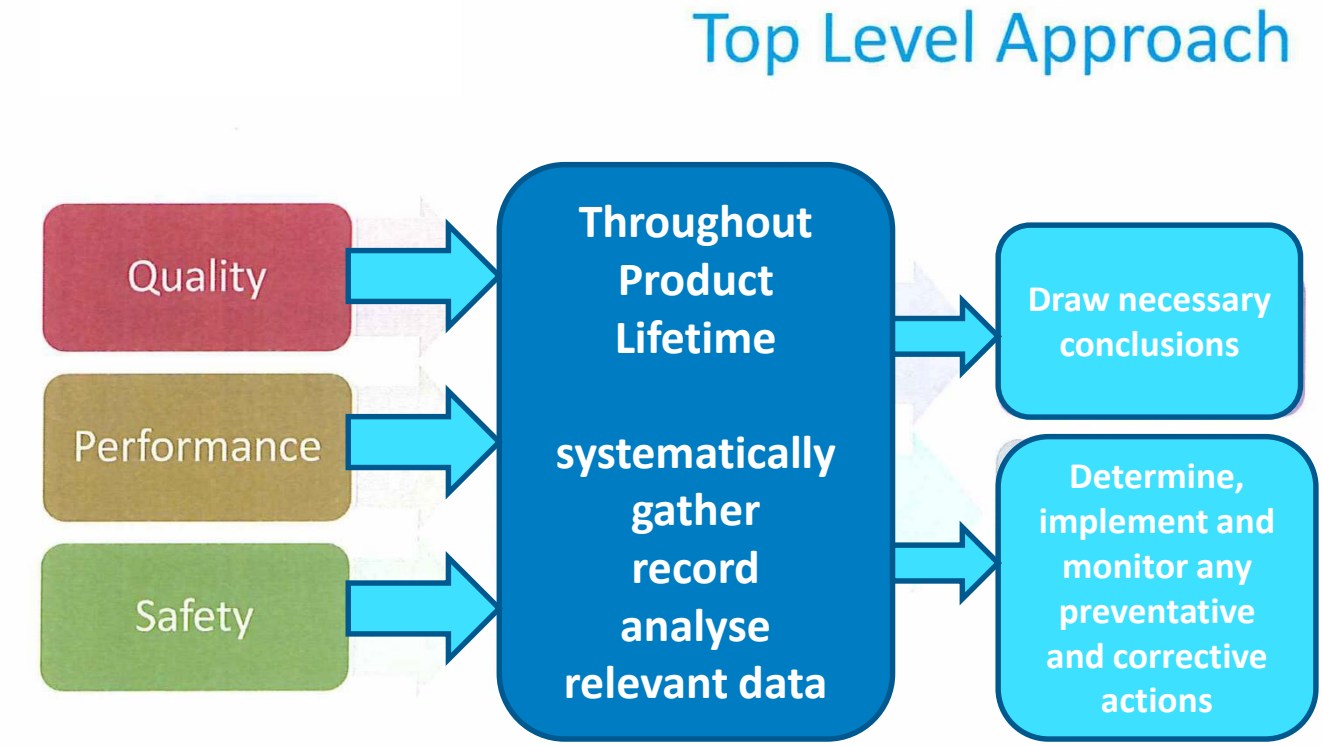

**Notified body assessment for ca. 85% of tests**

# Conformity Assessment by Notified Bodies & Expert Panels

## The Clinical Evaluation Consultation Procedure



# IV. Post-Market Surveillance System (proactive and preventative)




**For any device, proportionate to the risk classification and appropriate to the type of device, manufacturers shall establish, document, implement, maintain, update a post-Market Surveillance system which shall be an integral part of the Manufacturer's Quality Management System!**

# Impact of Post Market Surveillance requirements

**All** classes of devices must have a **POST-MARKET PERFORMANCE FOLLOW-UP PLAN**:

- **Classes A and B** must have an updated Post-Market Surveillance report which is available ***on request***;
- **Classes C and D** must have a Periodic Safety Update Report and a Performance Evaluation Report – both to be updated when necessary but ***at least annually***.

**IMPACT** on additional costs and training of staff, plus time to complete reports.

# V. UDI & Eudamed database

- UDI: Unique Device Identification!
- The EU system will hopefully be similar to the US system but there will be a separate EU database with potentially different data requirements.
- The manufacturer will need to notify all products to the Eudamed database and keep it updated.
- Importers will need to add their details to the product registration.
- Concerns over the speed of development & implementation of Eudamed database.

**Impact to industry** around the time and cost of inputting all the required data, and keeping it updated.

# VI. IVD Specific Issues:
## Preambule 29 in IVDR 2017/746

**Health institutions** should have the possibility of manufacturing, modifying and using **in-house tests** 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.

**"IN HOUSE" TESTS ARE EXEMPTED!**

# Requirements for In-House Tests

1. Manufacture and use within only **one** institution („legal entity“);

2. Implementation of appropriate **quality management systems**;

3. Compliance with **EN ISO 15189 or** further **national requirements** (e. g. accreditation);

4. **Documentation** that the health facility has given due consideration as to whether 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**;

# Requirements for In-House Tests

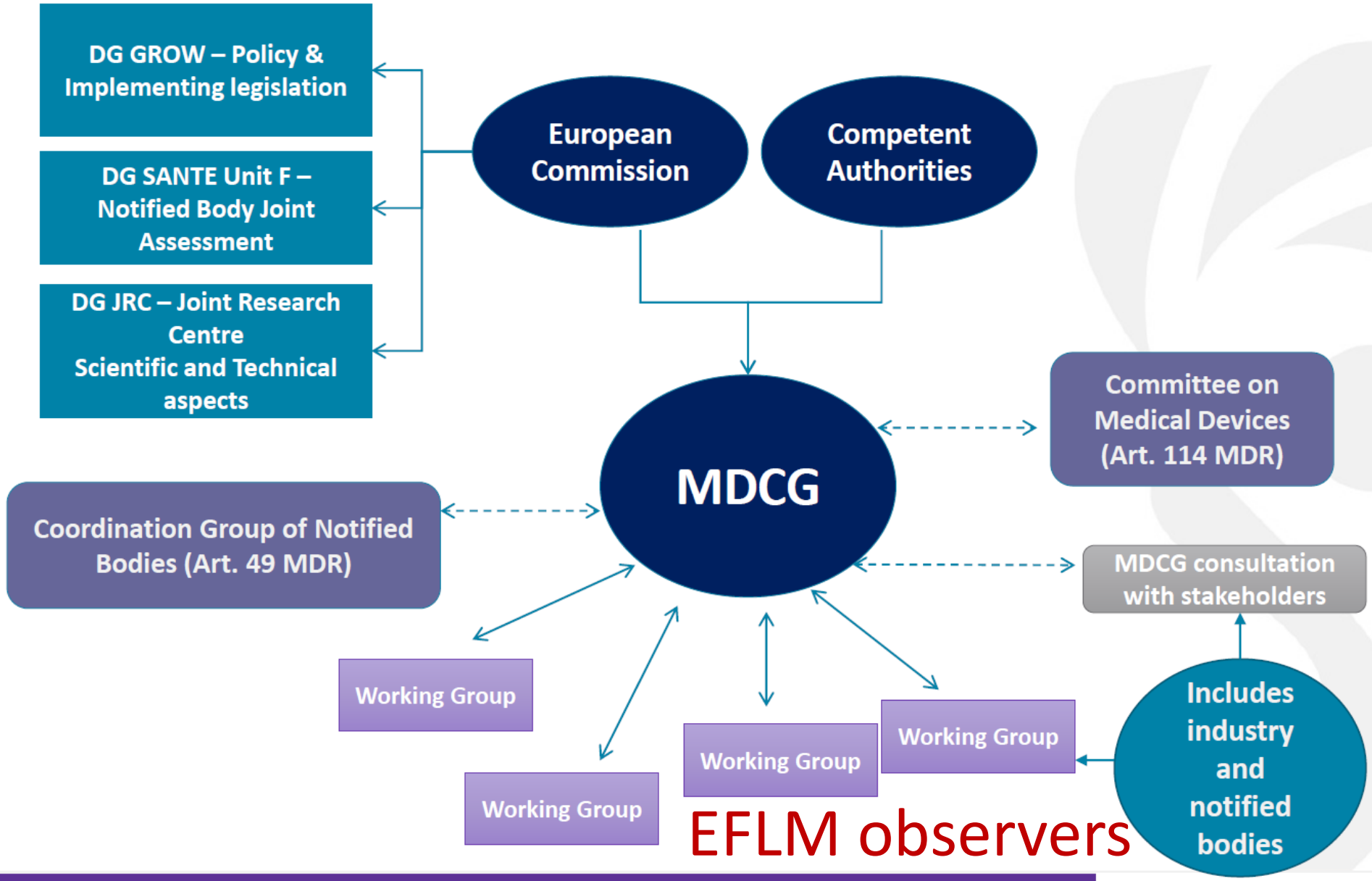
5. Upon request of the competent authority: **information** regarding the use of the in-house devices including a justification for manufacture, modification, use;

6. **Publicly available declaration of conformity** with product details;

7. For IVDMD of **class D**: complete and **detailed validation documentation** that enables the competent authority to assess whether the requirements are met;

8. **Product monitoring**

# D. Organisation at EU level



# How to make IVDR "operational"?

## Implementing and Delegated Acts

- Many instances of Delegated Acts and Implementing Acts necessary to make IVDR "operational"
- Unclear when these will be available…


e.g:

- Regulatory status of groups of products
- Common Specifications
- Format of Summary of Safety and Performance (SSP)
- UDI
- EUDAMED
- List of NBOG codes
- NB designation procedure

# MDCG guidance

Regulatory Focus™

Regulatory Focus™ > News Articles > 2019 > 10 > MDR/IVDR Guidance: MDCG Explains What's Coming

## MDR/IVDR Guidance: MDCG Explains What's Coming

Posted 25 October 2019 | By Zachary Brennan

The European Commission's Medical Device Coordination Group (MDCG) on Friday unveiled its plans for releasing almost 50 future guidance documents related to the Medical Devices Regulation (MDR) and the In Vitro Diagnostic Regulation (IVDR), with the bulk of the new guidance coming on the oversight of notified bodies (NBs) and clinical investigations and evaluation (CIE).

The list also notes that much of the guidance will be endorsed by the MDCG later this year or in 2020, although for more than 20 guidance documents, the timing is to be decided.

So far, the group has released guidance on NBs, Eudamed, Article 54(2) of MDR, transitional provisions, a new summary of safety and clinical performance, persons responsible for regulatory compliance and others.

# Notified body designation under IVDR

DEKRA Services Kontakt

DEKRA Certification Deutschland / News - Neuigkeiten aus allen Branchen / DEKRA Becomes First Notified Body in Europe for In-Vitro Diagnostics under New IVD Regulation


16 OKT 2019

DEKRA Certification GmbH, based in Stuttgart, is now the first company to be listed in the European Commission's NANDO database in accordance with EU Regulation (EU) 2017/746 on in-vitro diagnostics. The regulation came into force in 2017 and will apply on May 26, 2022. The procedure to be approved as a Notified Body is extremely complex and took around two years.

In the new Regulation (EU) 2017/746, the provisions on EU market access have been made considerably stricter. Several products for which a self-declaration was previously sufficient will require approval by a Notified Body from 2022 onward. There are also stricter rules on documentation, clinical evaluation and monitoring.

# EC Call for Experts for assessing class D tests

**Deadline 10 november 2019**

# EUDAMED database

## European database on medical devices (EUDAMED)

**The new regulations on medical devices (MDR) and on in vitro diagnostic medical devices (IVDR) establish a much wider EUDAMED database than the existing one under the current directives (Eudamed2).**

Currently, the EC database on medical devices, Eudamed2, is a secure web-based portal. It is a central repository for information on market surveillance exchanged between national competent authorities and the Commission. Its use is restricted to national competent authorities, it is not open for consultation and is not publicly accessible.

However, the new medical devices regulations contain important improvements including a much larger EUDAMED database. The new rules will only apply after a transitional period

- 3 years after entry into force for the regulation on medical devices (spring 2020)
- 5 years after entry into force for the regulation on in vitro diagnostic medical devices (spring 2022)

We expect the new EUDAMED database to be in production and available to the public in 2020. It will contain different modules on actors, UDI & devices, notified bodies & certificates, vigilance, clinical investigations & performance studies and market surveillance. It will be multipurpose. It functions as a registration system, a collaborative system, a notification system, a dissemination system (open to the public), and will be interoperable.

# E. Preparing the transition for IVDR compliance

CAMD
Competent Authorities for Medical Devices

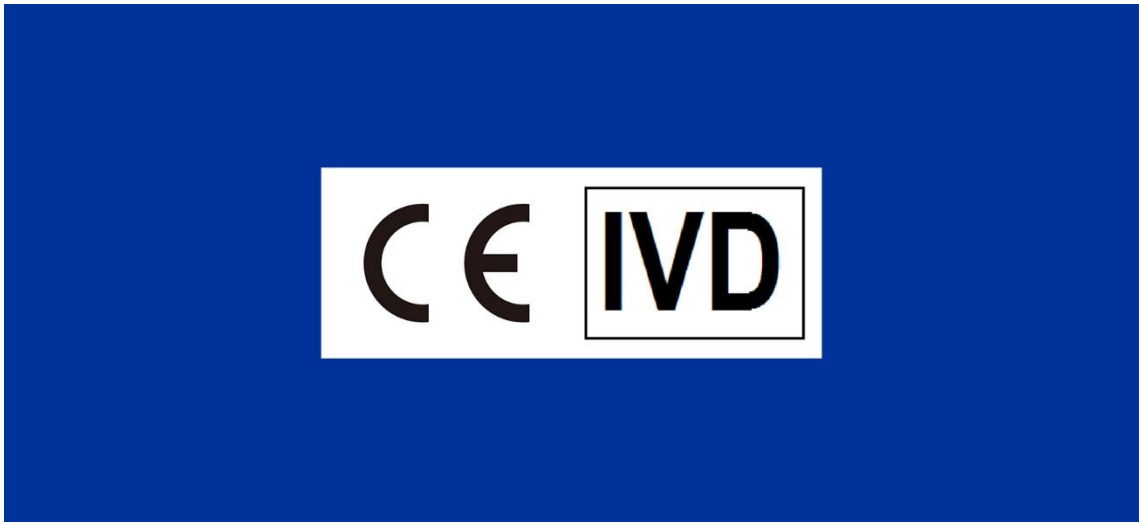
**CAMD Implementation Taskforce**

Medical Devices Regulation/In-vitro Diagnostics Regulation (MDR/IVDR) Roadmap

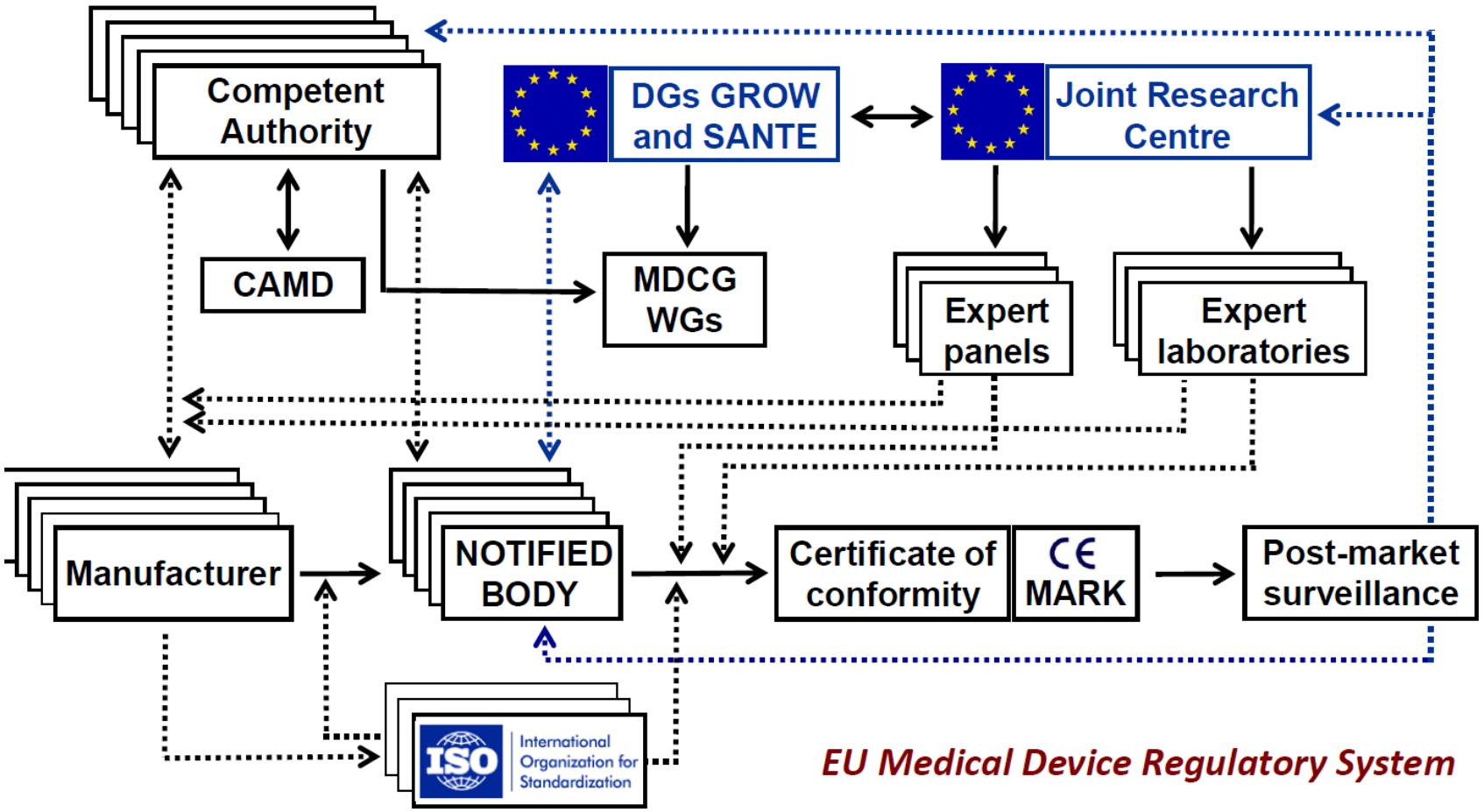

**https://www.camd-europe.eu/regulatory/medical-devices-regulation-vitro-diagnostics-regulation-mdr-ivdr-roadmap**

# Preparing the transition for IVDR compliance

## From the perspective of IVD-manufacturers



# EU Medical Device Regulatory System



http://www.medtecheurope.org/sites/default/files/resource_items/files/MTE_IVDR_Flowchart-Dec-2017_FINAL.pdf

# Design

Defines

Define Properties of the IVD

**IVD Intended Purpose**

- Article 2(12) Annex I Section 20.4.1(c)
  - What is detected / measured
  - Function
  - Specific info to be provided
- Self-test
- Near-patient test
- Intended User
- Instrument
- Companion Diagnostic
- Software

Classification (Article 47, Annex VIII)

Determines

Define Applicable Requirements for the MANUFACTURER's Processes

**Basis for Requirements Checklist**

**Annex I**

| | |
|---|---|
| Annex I Section 1 | General Design and Safety requirements |
| Annex I Section 3 | Risk Management System |
| Annex I Section 4 | Risk Control Measures |
| Article 8 Article 9 | Use of Harmonised Standards / CS |

+

Define Applicable Requirements For the DEVICE

**Annex I**

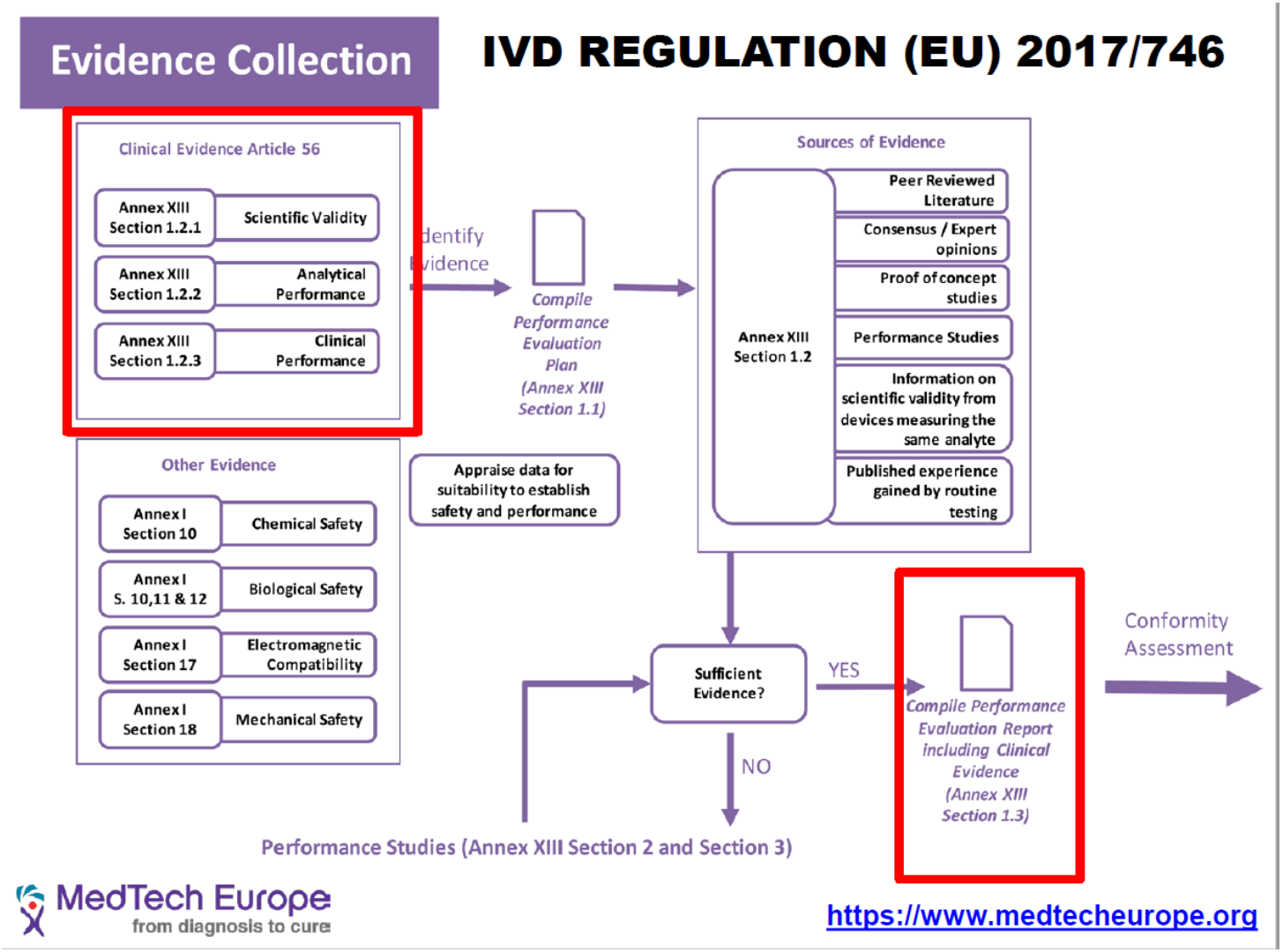
| | |
|---|---|
| Annex I Section 9 | Performance Characteristics |
| Annex I Section 10 | Chemical, Physical & Biological Properties |
| Annex I Section 11 | Infection & Microbial Contamination |
| Annex I Section 12 | Material of Biological Origin |
| Annex I Section 13 | Interaction with the Environment |
| Annex I Section 14 | Measuring Function |
| Annex I Section 15 | Protection Against Radiation |
| Annex I Section 16 | Software |

# Obligations of Manufacturers

**Manufacturer Obligations**

| | |
|---|---|
| Article 10 Para 2 | Risk Management System |
| Article 10 Para 3 | Performance evaluation incl. PMPF |
| Article 10 Para 4 | Technical documentation |
| Article 10 Para 5 | Conformity assessment, DoC and CE marking |
| Article 10 Para 6 | UDI assignment |
| Article 10 Para 7 | Availability of Technical Doc, Cert. and DoC |

# IVDR 2017/746:
# key change: Clinical Evidence requirement



# Untenable Transition to EU MDR/IVDR!?

RF Regulatory Focus™

Regulatory Focus™ > News Articles > 2019 > 4 > MedTech Europe Warns Over 'Untenable' Transition to EU MDR/IVDR

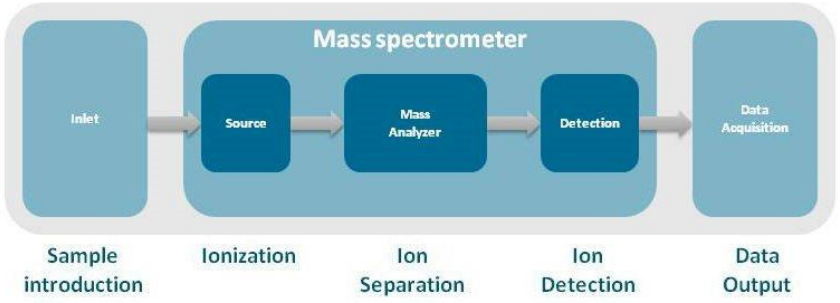
## MedTech Europe Warns Over 'Untenable' Transition to EU MDR/IVDR

Posted 17 April 2019 | By Ana Mulero

MedTech Europe sent an open letter to the European Commission (EC) on Monday to urge immediate action on implementing the new medical device and IVD regulations as the transition is becoming "clearly untenable."

The letter from the trade association's CEO Serge Bernasconi underscores the growing urgency and need for the EC and member states to finish what they started in 2017 with the EU's medical device and *in vitro* diagnostic regulations (MDR/IVDR). The letter highlights the current lack of progress to implement both regulations, while warning of potential access issues to medical technologies in the EU.

# From the perspective of lab professionals/ LDTs



# A number of important requirements for running LDTs!

## Quality Management System (QMS)/ISO 15189
## Risk management
## Clinical evidence
## Proof of non-equivalence!

**The laboratory that uses the LDTs is responsible for the justification that the LTD is required** for optimal patient care, and that there is no equivalent CE-IVDs available that can be used instead.

This is a continuous responsibility, so regular monitoring and evaluation of new CE-IVDs is mandatory under the IVDR for the lifetime of the LDT. Therefore, publication of the results from comparisons between IVDs and LDTs will be worthwhile in this process.

The **European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) WG on Test Evaluation** has developed a **TOOLBOX to substantiate the justification of the need for LDTs in a standardized and rational manner**:

- Identification of unmet clinical needs according to a structured checklist;
- Definition of the target population;
- Description of the specific clinical pathway, including a detailed specification of the LDT.

## Evaluation of use:

guidance for evaluation of use of LDTs can be found in Article 78-79 and Annex III (about PMS).

# Toolbox of the EFLM Working group on Test Evaluation


https://www.eflm.eu/site/page/a/1158

# Toolbox of the EFLM Working group on Test Evaluation

## Working Group: Test Evaluation

Back Home

Back to the main page of the WG-TE

### Resources / Educational Material

**Practical toolbox**

**Interactive unmet needs checklist.**

The unmet clinical needs checklist produced by the EFLM Test Evaluation Working Group (WG-TE) is a practical tool, with worked examples, to assist researchers, laboratory professionals and the In Vitro Diagnostic (IVD) industry working with clinicians, to identify unmet clinical needs and improve the targeted development of IVD medical tests for improved health outcomes. The tool is aligned with the Institute of Medicine (IOM) recommendations and the US Food and Drug Administration (FDA) and Conformité Européene (CE) regulatory framework requirements. In collaboration with the EFLM Working Group for Distance Education and e-Learning (WG-DE), it was developed an interactive version of the checklist, available on the EFLM e-Learning platform: https://elearning.eflm.eu/course/view.php?id=11. The platform also contains a short video showing how to use the interactive checklist.

**Articles**

**Practical guide for identifying unmet clinical needs for biomarkers.**
*Monaghan P, Robinson P, Rajdl D, Bossuyt PMM, Sandberg S, St John A, O'Kane M, Lennartz L, Roddiger R, Lord SJ, Cobbaert CM, Horvath AR*
eJIFCC 2018;29;129-37
Click here to download the paper

**Biomarker development targeting unmet clinical needs**
*Monaghan P, Lord SJ, St John A, Sandberg S, Cobbaert CM, Lennartz L et al. for the EFLM Working Group onTest Evaluation*
Clin Chim Acta 2016;460:211-9
Click here to download the paper

# Clinical Pathway Mapping Templates for LDTs


CLINICAL PATHWAY MAPPING (CHECKLIST STEP 1)

**Target population & setting**

(Primary care [GP, community], secondary, tertiary care,)

Country/health care system

- ☐ Primary care
- ☐ Secondary care
- ☐ Tertiary care

**Current test(s) and clinical assessment tools**

- ☐ Diagnosis
- ☐ Prognosis
- ☐ Screening
- ☐ Prediction
- ☐ Other (please specify)

**New Biomarker intended use (role):**

- ☐ Replacement
- ☐ Add-on
- ☐ Triage
- ☐ Other (please specify)

**Management decision**

(Therapeutic intervention, other)

Test Positive: Test negative:

**Health Outcomes:**

- ☐ Mortality
- ☐ QoL (pain,employment)
- ☐ Other (Please specify)

Potential benefits for patient/physician:

Potential harms for patient/physician:

**Unmet needs:**


CLINICAL PATHWAY MAPPING (CHECKLIST STEP 3)

Current practice | Intended use of new biomarker / LDT

Target population & setting

Current test(s) and clinical assessment tools

New Biomarker intended use (role):

- ☐ Replacement
- ☐ Add-on
- ☐ Triage
- ☐ Other (please specify)

Management decision

Test Positive | Test Negative

Management decision

Test Positive | Test Negative

Health Outcomes

Benefits:

Harms:

Unmet needs:

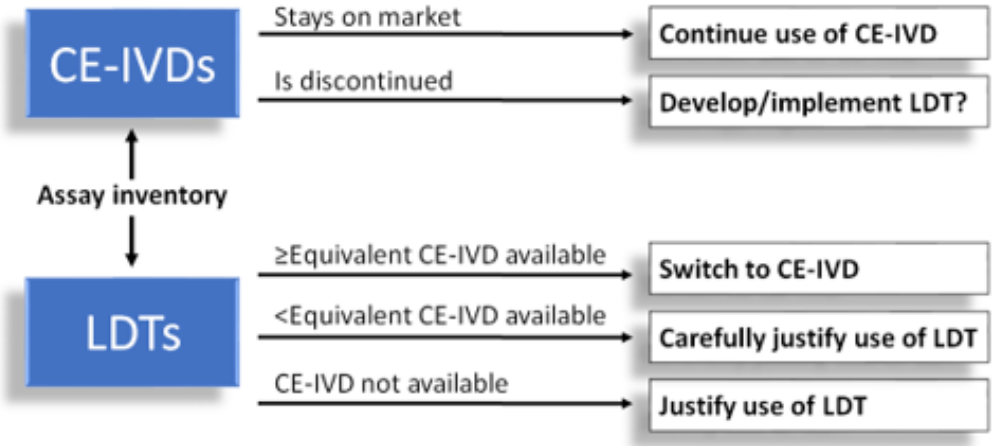
Health Outcomes

Potential Benefits | Potential Harms

# Recommendations for diagnostic laboratories & consortia

- Make sure you maintain/obtain ISO 15189 accredititation
- Make a test inventory & decide on CE-IVD versus LDT options

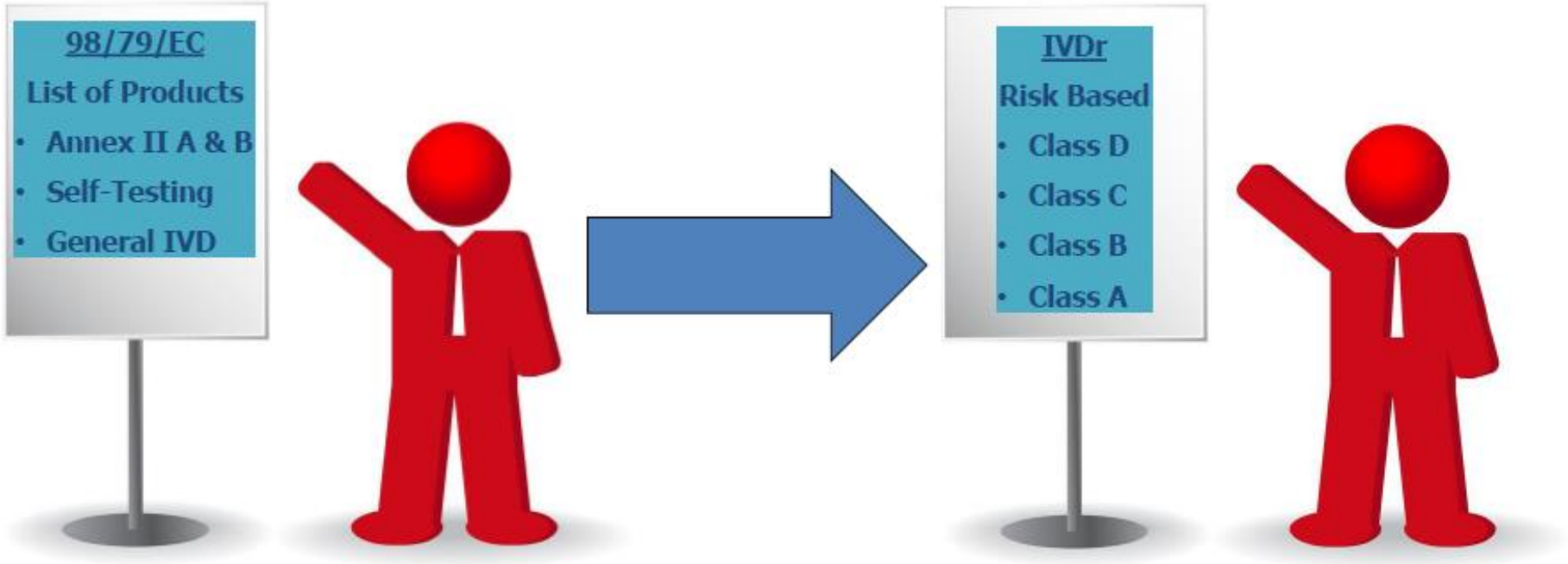
## Test Inventory Decision Tree




- Make sure you can justify use of your LDTs
- Make/stay actively informed about templates/guidance for IVDR and documentation for LDTs
- Get in touch with your national CA

# F. Conclusions 1/3

## IVDR: from a “good will” approach to “legal” Regulation




From ~85% self-declaration to ~15%;
From ~15% conformity assessment by notified bodies to ~85%.

# F. Conclusions 2/3

The IVDR is vastly more “legal” in nature than its predecessor, which took more of a “good will” approach in many ways. This has **CONSEQUENCES FOR STAFFING** at CAs, NBs, EOs, Medtech Europe & IVD-manufacturers included.

The Regulation **CHANGES THE EUROPEAN REGULATORY ENVIRONMENT** as

1. more stringent clinical data requirements,
2. extended data management,
3. more complex conformity assessment procedures (particularly for high-risk tests),
4. and product liability and penalties will be introduced.

**NoBo’s are already signaling they will not be able to process all this extra work,** which may lead to compliant devices losing access to the European market.

# F. Conclusions 3/3

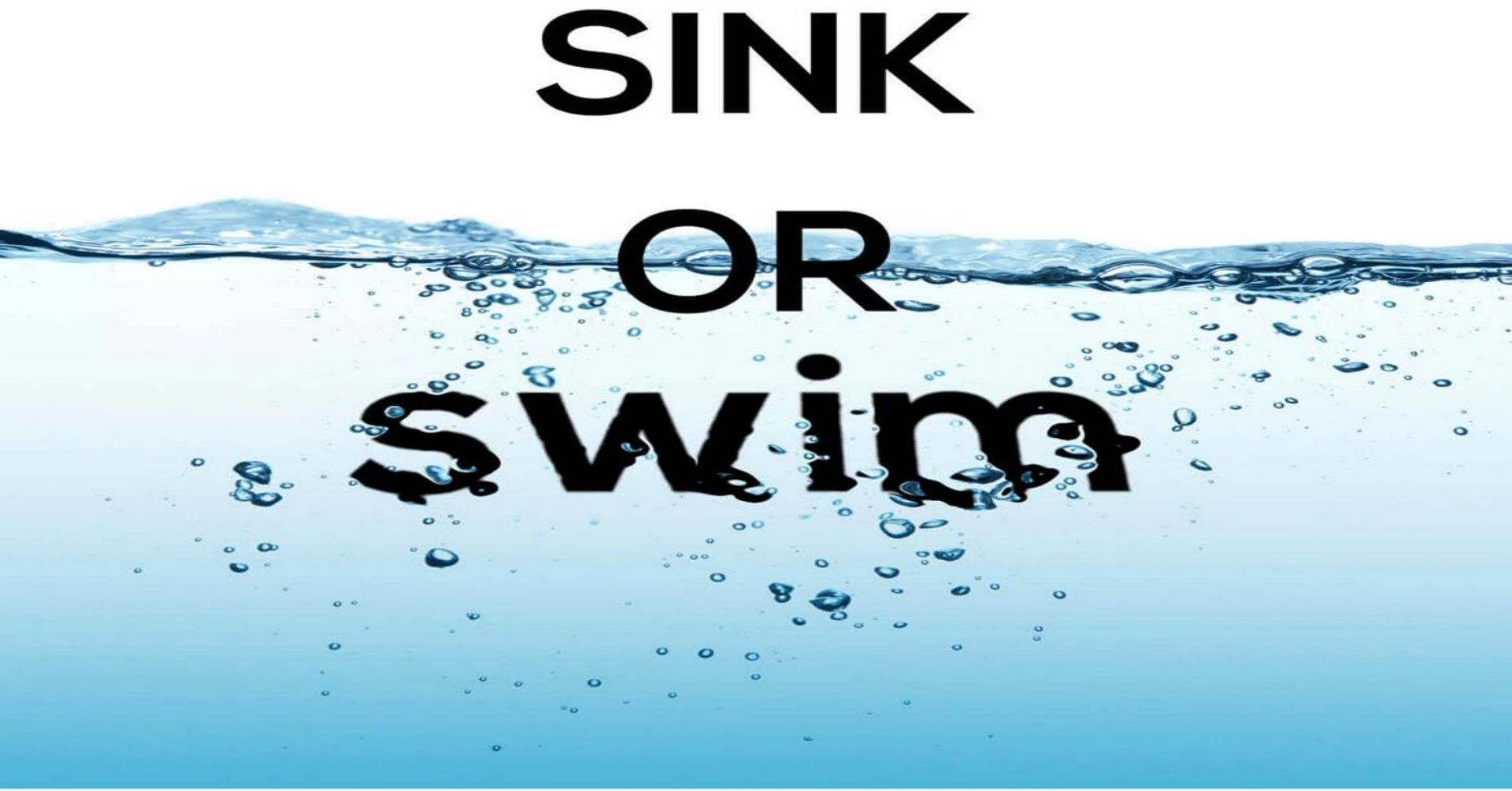
## Health Institution Exemption for in-house tests (Article 5 of IVDR)

Devices/LDTs that are manufactured or modified and used **WITHIN** health institutions shall be considered as having been put into service.

**THE REQUIREMENTS IN THE IVDR DO NOT APPLY TO LDTs PROVIDED THAT CERTAIN CONDITIONS ARE MET**, including:

- health institutions ensure that the relevant general safety and performance requirements are followed (Annex I);
- an appropriate quality management system is established;
- the health institution **justifies** that the target group's specific needs cannot be met by an equivalent device on the market;
- information is made available to competent authorities on request;
- a declaration with certain details is made publicly available;
- reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

# IVDR preparations: up or out, sink or swim!



# Thanks for your attention

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE